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Copper-Catalyzed Cyanoalkylation of Amines via C−C Bond Cleavage: An Approach for C(sp^3)−N Bond Formations

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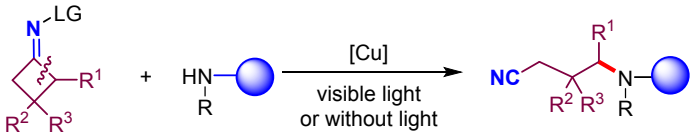


- *(hetero)aromatic amines*
- *aromatic N-heterocycles*
- *sulfonamides*
- *aliphatic amines & amino acid esters*
- *natural products & drugs*

>75 examples
up to 93% yield

ABSTRACT

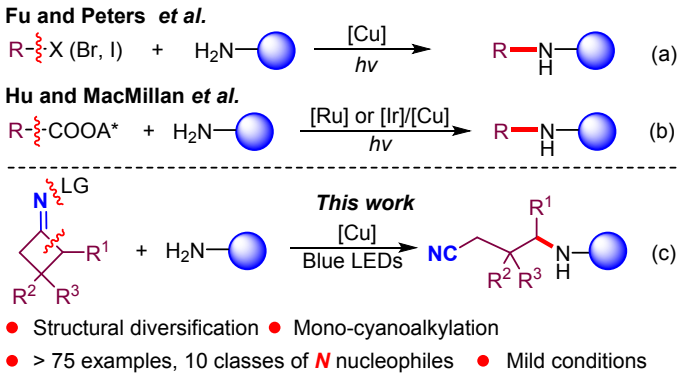
An efficient copper-catalyzed cyanoalkylation of amines via C−C bond cleavage has been demonstrated. Distinctive features of this procedure involves mild conditions, broad range of nitrogen nucleophiles, high selectivity and good functional group tolerance, thus providing a useful approach for the C(sp^3)−N bond formations. Most importantly, this protocol is applicable to late-stage functionalization of natural products, amino acid esters and drugs. Mechanistic studies suggest that radical intermediate was involved in this transformation.

INTRODUCTION

Amines represent an important class of structural motifs, which exist widely in natural products, pharmaceuticals, agrochemicals and materials.[1] Thus, the construction of C−N bonds has attracted much attention of chemists and has become a hot topic in organic synthesis. In this field, transition-metal catalyzed cross coupling of aryl electrophiles with amines has proven to be a powerful tool for the C(sp^2)−N bond formations, such as Ullmann coupling, Buchwald-Hartwig reaction, and Chan-Lam amination.[2] Apart from the traditional S_N2 alkylation of amines, olefin hydroamination, reductive aminations and

others,[3] transition-metal catalyzed amination of alkyl electrophiles (halides and pseudo halides) has also been developed as an efficient method for the C(sp^3)–N bond formations.[4] However, this method is still challenging due to the facile β-hydrogen elimination of metal alkyl intermediates and difficulty in C(sp^3)–N reductive elimination. Recently, the combination of photoredox and copper catalysis has emerged as an excellent alternative for the transition metal-catalyzed amination reactions.[5,6] For instance, Fu and Peters et al demonstrated several photoinduced, copper-catalyzed amination of alkyl halides using carbazoles, carboxamides, indoles, carbamates, and aliphatic amines as nitrogen nucleophiles (Scheme 1, route a).[5] Moreover, they also reported an intramolecular decarboxylative amination of alkyl NHPI esters under this dual catalytic system.[6a] Very recently, the groups of Hu and MacMillan disclosed the intermolecular decarboxylative amination of alkyl NHPI esters and alkyl carboxylic acids via synergetic photoredox and copper catalysis, respectively (Scheme 1, route b).[6b-d] In these C(sp^3)–N bond formation reactions, alkyl halide, redox-active alkyl NHPI esters and iodonium carboxylates have been developed as efficient alkyl sources. Although remarkable advances have been made, it is still necessary and highly desirable to explore elegant catalytic systems, functionalized

Scheme 1 C(sp^3)–N Couplings via Synergetic Photoredox and Copper Catalysis

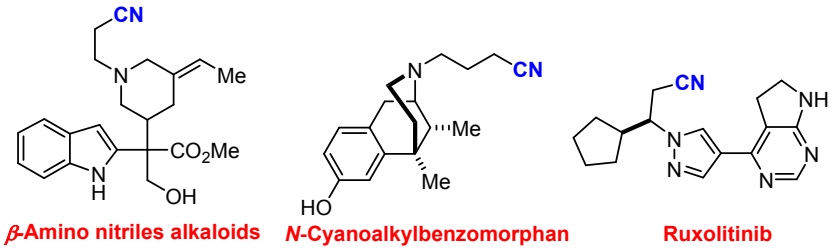


alkyl electrophiles as well as broad amine nucleophiles to achieve the structurally diverse alkyl amine synthesis.

In recent years, the radical carbon-carbon bond cleavage of strained rings has become an efficient strategy for carbon-carbon and carbon-heteroatom bond formations.[7] Since the pioneering work of Forrester, Zard, Uemura *et al.*[8] the iminyl radical-triggered carbon-carbon bond cleavage of cycloketone oxime derivatives has become a powerful tool to construct C(sp^3)−C and C(sp^3)−Y (Y = O, S, Se, Te, X or B) bonds.[9,10] In these transformations, the reactive cyanoalkyl radicals generated *in situ* were trapped by a variety of radical acceptors to deliver structurally diverse alkylnitriles through transition-metal catalysis, photocatalysis, and even transition-metal free systems. Recently, we wondered whether the C(sp^3)−N bond formation can be accessible without recourse to harsh conditions, complex catalytic systems or expensive metals. To achieve this, several hurdles should be overcome simultaneously: (i) β-hydride elimination of cyanoalkyl metal complex;[11] (ii) fragmentation-rearrangement of cycloketone oxime esters;[10b-d] (iii) neophyl rearrangement, reduction and oxidation of cyanoalkyl radical.[10e-f] As our ongoing interest in C−C bond cleavage, we set out to challenge the C(sp^3)−N bond coupling of cycloketone oxime esters with amines, aiming at incorporating the important cyanoalkyl moieties into structurally diverse nitrogen-containing molecules, especially bioactive natural products and drugs (Figure 1).[12] Inspired by the previous fascinating works,[5,6] we herein describe a room-temperature, copper-catalyzed C−C bond cleavage/amination of cycloketone oxime esters (Scheme 1, route c). A variety of (hetero)aromatic amines, aromatic *N*-heterocycles, sulfonamides and even aliphatic amines were amenable for this cyanoalkylation

transformation. Furthermore, this protocol can be applied successfully to the late-stage functionalization of some natural products, amino acid esters and drugs. It is worth noting that visible-light irradiation was indispensable for the success of this reaction in some cases.

Fig. 1 Natural Products and Drugs Containing Alkylnitrile Moieties

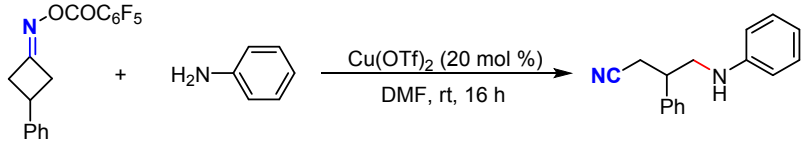


RESULTS AND DISCUSSION

We commenced our study by evaluating the coupling of various cyclobutanone oxime esters **1** with aniline (**2a**) (see the Supporting Information for details). Primary optimization demonstrated that treatment of cyclobutanone *O*-perfluorobenzoyl oxime (**1a**) with aniline (**2a)** in the presence of 20 mol % $Cu(OTf)_2$ in DMF under room temperature led to the desired mono-cyanoalkylated aniline **3a** in 82% yield (Table 1). Control experiment indicated that the copper catalyst was essential for this transformation (entry 1). Thus, other copper catalysts such as $Cu(OAc)_2$, CuI and CuOTf were tested. But all of them were less effective than $Cu(OTf)_2$, affording the product **3a** in 37-66% yields (entries 2-4). The addition of bases did not improve the yield of **3a** (entries 5-7). Solvent screenings revealed that a mixture of DMF and H_2O (1:1) was superior to other solvents (entries 8 and 9). Additionally, the reaction could give a comparable yield of **3a** in the dark as in ambient light, which indicates that light is unnecessary for the reaction of **1a** with **2a** (entry 10). Notably, this reaction can be easily scaled up to 3 mmol with the high efficiency (entry 8). It is worth mentioning that the pentafluorobenzoic acid could be recovered in 65% after the reaction,

which would significantly reduce the costs and waste of this transformation.

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**, 82%

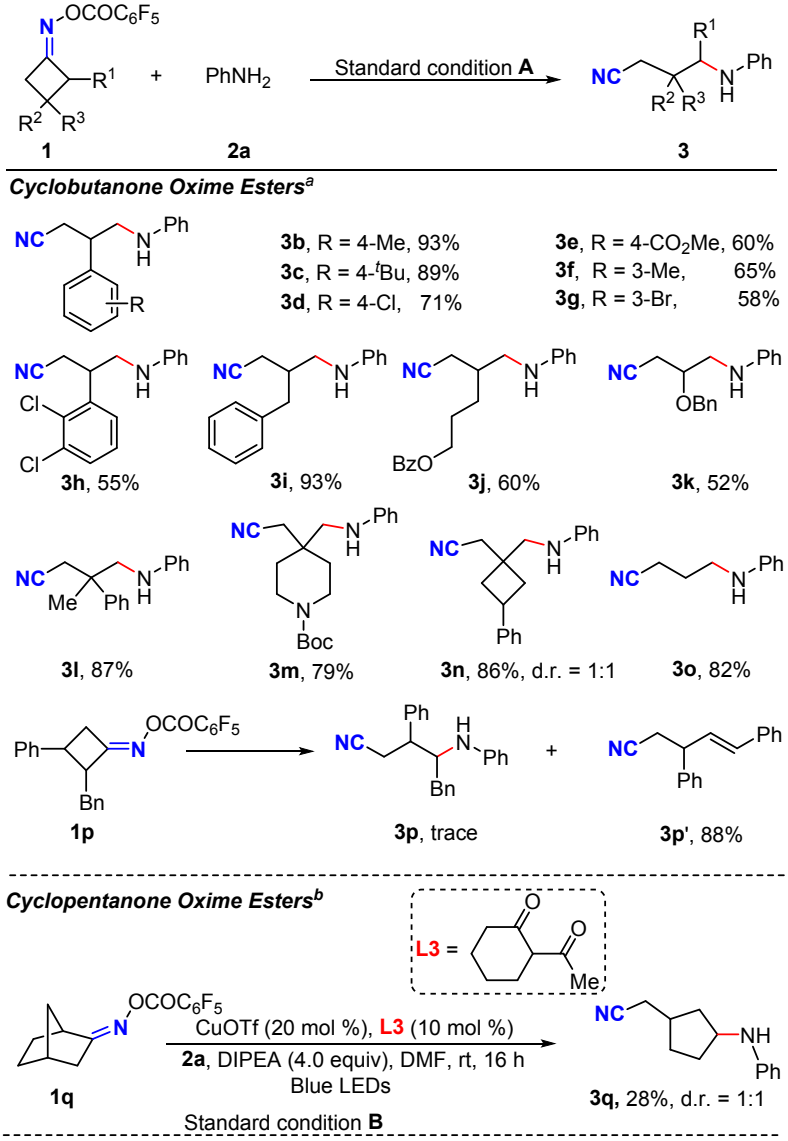
Entry	Deviation from above	Yield[b] (%)
1	no $Cu(OTf)_2$	n.r.[c]
2	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	37
3	CuI instead of $Cu(OTf)_2$	50
4	CuOTf instead of $Cu(OTf)_2$	66
5	1.2 equiv LiO^tBu added	63
6	1.2 equiv $K_2C_2O_4 \cdot H_2O$ added	82
7	1.2 equiv DIPEA added	75
8	DMF:H_2O (1:1) instead of DMF	88 (76[d])
9	H_2O instead of DMF	10
10	DMF:H_2O (1:1), in the dark	85

[a]Standard conditions: 20 mol % of $Cu(OTf)_2$, **1a** (0.20 mmol, 1.0 equiv), **2a** (0.40 mmol, 2.0 equiv), DMF (2.0 mL), at room temperature for 16 h, under N_2. [b]Yields of isolated product. [c]n.r.= no reaction. [d]The reaction was scaled up to 3.0 mmol, and the pentafluorobenzoic acid was recovered in 65% yield.

With the optimal conditions in hand, we investigated the generality and limitations of this C−C bond cleavage/C−N bond formation reaction. A variety of cyclobutanone oxime esters reacted efficiently with aniline **2a** to give the corresponding secondary amines **3b-o** in moderate to good yields (Scheme 2). 3-Substituted oxime esters bearing aryl, benzyl, alkyl or ether groups converted smoothly to the target products **3b-k** in moderate to excellent yields. Functional groups such as CO_2Me, Br, BzO and OBn groups were well-tolerated. 3,3-Disubstituted substrates, even the spirocyclic substrates (**1m, 1n**) also delivered the desired products **3l-n** in good yields. The *N*-Boc group in substrate was compatible with the reaction conditions (**3m**). Cyclobutanone oxime ester **1o** derived from simple cyclobutanone also furnished the product **3o** in 82% yield. However, the 2,3-disubstitutedoximeester **1p** failed to give the expected amine **3p**, instead of the *β*-hydrogen elimination product **3p'** in 88% yield.[11] The less strained norcamphor oxime ester **1q** were ineffective at the present conditions. Luckily, the anticipated product **3q** could be obtained

through copper catalysis upon visible-light irradiation, albeit in somewhat low yields.

Scheme 2 Scope of Cyclobutanone Oxime Esters

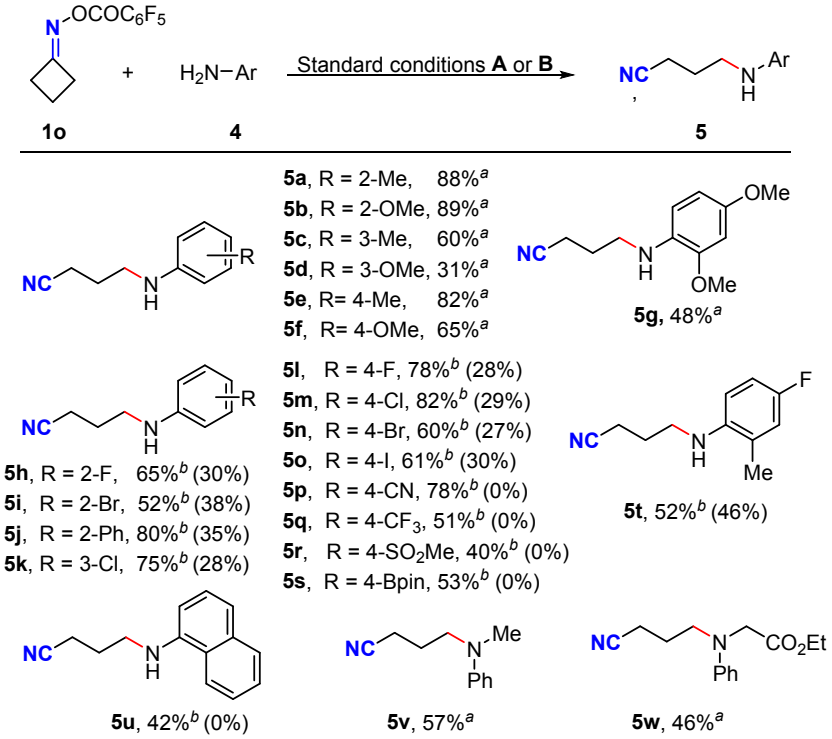


[a]Standard condition A: 20 mol % of $Cu(OTf)_2$, **1** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), DMF/H_2O (1:1, 2 mL), rt, 16 h, under N_2, isolated yield. [b]Standard condition B: 20 mol % of CuOTf, **L3** (10 mol %), **1q** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), DIPEA (4.0 equiv), DMF (2 mL), rt, 10 W blue LEDs for 16 h, under N_2, isolated yield.

Then, we evaluated the scope of amine nucleophiles using **1o** as cyanoalkylation reagent under this copper catalytic system. Satisfactorily, a variety of aromatic amines bearing electron-rich at *ortho*-, *meta*-, and *para*-position of the phenyl ring worked well with **1o** to afford the desired products **5a-g** in moderate to good yields (Scheme 3). However, the electron-poor aromatic

amines were less or inefficient under reaction conditions **A**. Treatment of oxime ester **1o** with

Scheme 3 Scope of Aromatic Amines



[a]Standard condition **A**: 20 mol % of $Cu(OTf)_2$, **1o** (0.2 mmol, 1.0 equiv), **4** (0.4 mmol, 2.0 equiv), DMF/H_2O (1:1, 2 mL), rt, 16 h, under N_2, isolated yield. [b]Standard condition **B**: 20 mol % of CuOTf, **L3** (10 mol %), **1o** (0.2 mmol, 1.0 equiv), **4** (0.4 mmol, 2.0 equiv), DIPEA (4.0 equiv), DMF (2 mL), rt, 10 W blue LEDs for 16 h, under N_2, isolated yield. The yields of **5h-u** under condition **A** in parentheses.

4-aminobenzonitrile **4p** in the presence of 20 mol % of $Cu(OTf)_2$ in DMF/H_2O only furnished a trace amount of the desired product **5p**. Increasing the reaction temperature to 80 °C did not improve the yield of **5p**. Other ligands or bases were also tested, but none of them gave positive results. During optimization of the reaction conditions, unsaturated nitriles and γ-carboxylated alkyl nitriles were observed as by-products in some cases (see the Supporting Information for details).[10,11] After many trials, we found that the reactions proceeded efficiently in the presence of 20 mol % of CuOTf, 10 mol % of 2-acetylcyclohexanone (**L3**)[13] and 4.0 equiv of DIPEA under irradiation of 10 W blue LEDs to give the desired amines **5h-u** in moderate to good yields. It should be mentioned

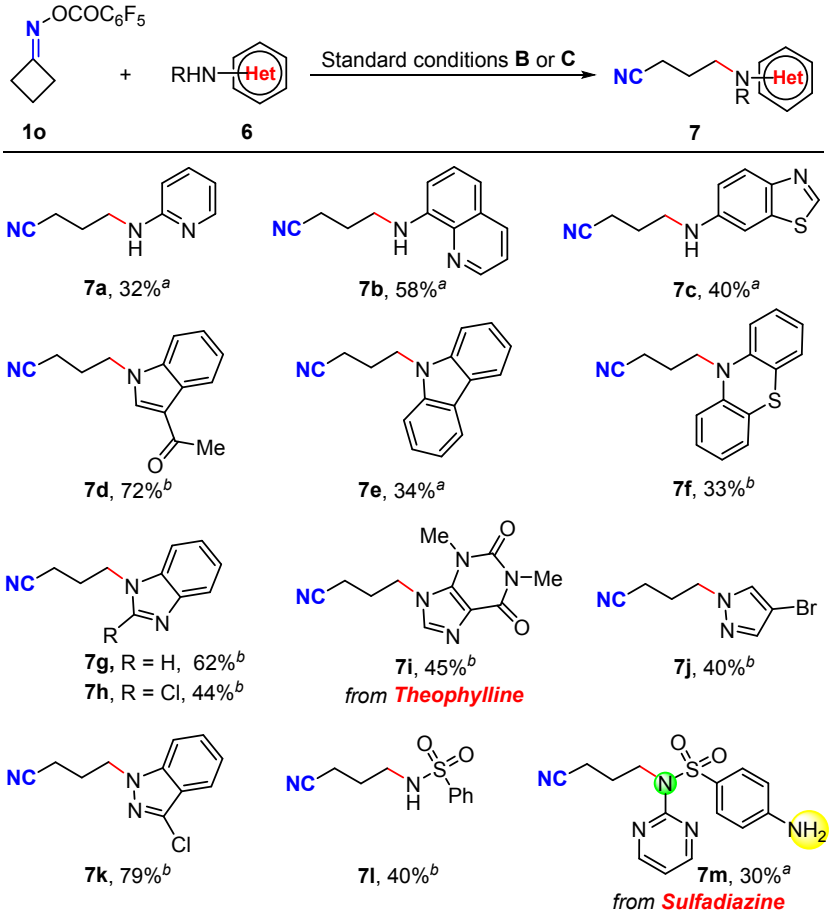
that the visible-light irradiation was necessary for good reaction efficiency of **1o** with electron-poor aromatic amines **4h-u** (Scheme 3), while any exogenous photosensitizer was not required. Notably, the synthetic important functional groups inlcuding Br, I, CN, SO_2Me and Bpin groups were survived well. Besides primary amines, the *N*-methylaniline **4v** also gave the corresponding tertiary amine **5v** in 57% yield. *N*-phenylglycine ethyl ester **4w** was also suitable substrate, affording the desired product **5w** in 46% yield. While the diphenylamine was invalid under the present conditions (not shown).

Furthermore, a range of structurally diverse heteroaromatic amines and aromatic *N*-heterocycles were subjected to this copper-catalyzed system (Scheme 4). Heteroaromatic amines such as pyridin-2-amine, quinolin-8-amineand benzo[*d*]thiazol-6-amine were efficient nitrogen nucleophiles, producing the secondary amines **7a-c** in moderate yields. In addition, weakly electrophilic aromatic *N*-heterocycles such as indole (**6d**), carbazole (**6e**), phenothiazine (**6f**), benzo[d]imidazole (**6g** and **6h**), pyrazole (**6j**) and indazole (**6k**) were also efficient, furnishing the corresponding cyanoalkylated products in acceptable yields under slightly modified reaction conditions. The theophylline **6i** could also be cyanoalkylated in 45% yield. In addition, the sulfonamide **6l** also provided the desired product **7l** in moderate yield. Unexpectedly, the sulfadiazine **6m** containing an amine group and an amide group reacted chemoselectively to give the **7m** as sole product in 30% yield, which is probably attributed to the pyrimidine substituent.

Encouraged by above results, we hope to extend this $C(sp^3)$–N bond-forming procotol to the more challenging aliphaticamines.[4-6] So far, catalytic direct mono-alkylation of

aliphatic amines has rarely been explored, mostly due to the issues of E2 side reactions and over-alkylation.[5d] Further investigation demonstrated that the cyanoalkylation of aliphatic

Scheme 4 Scope of Heteroaromatic Amines and Aromatic *N*-Heterocycles

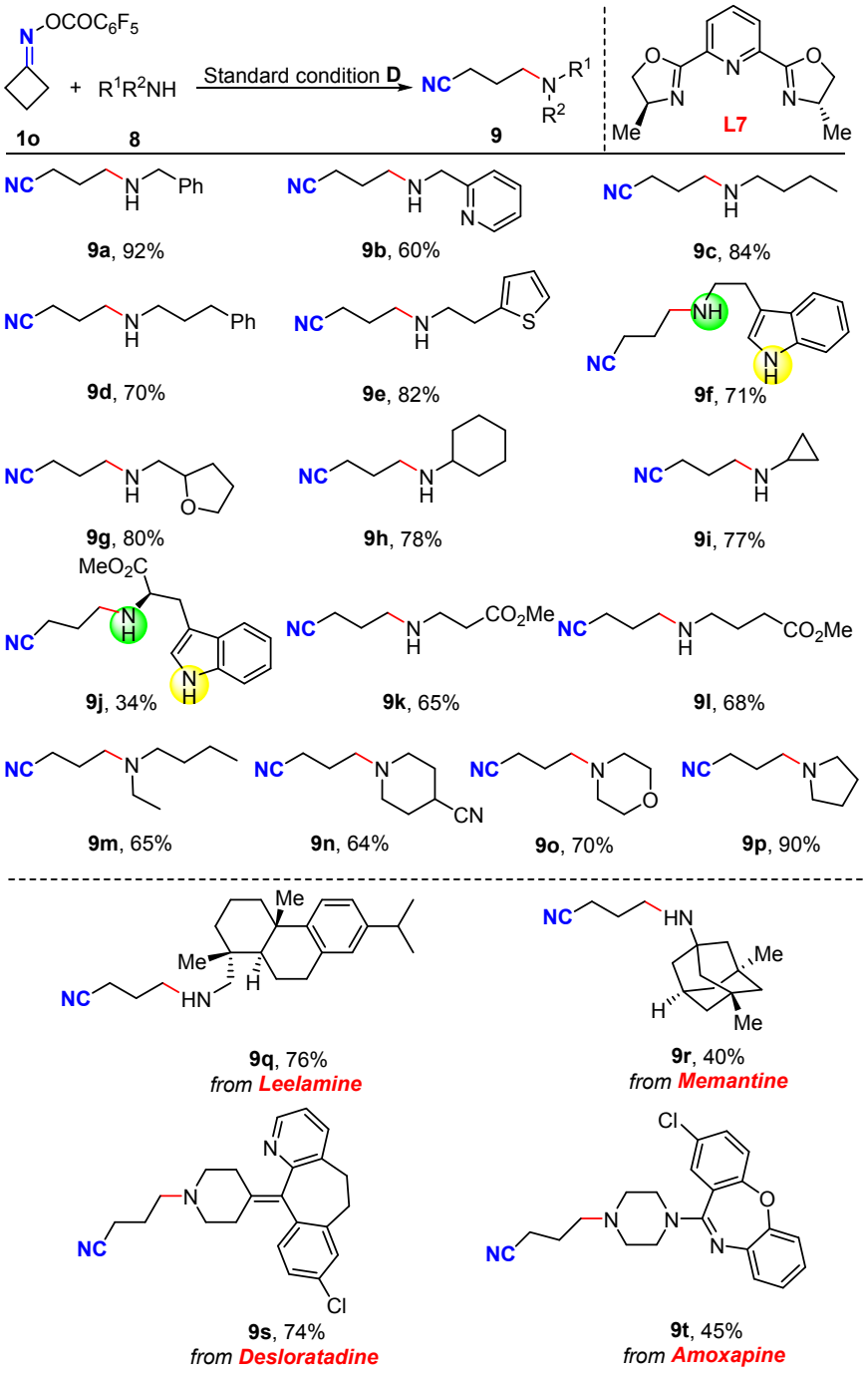


[a]Standard condition **B**: 20 mol % of CuOTf, **L3** (10 mol %), **1o** (0.2 mmol, 1.0 equiv), **4** (0.4 mmol, 2.0 equiv), DIPEA (4.0 equiv), DMF (2 mL), rt, 10 W blue LEDs for 16 h, under N_2, isolated yield. [b]Standard condition **C**: 20 mol % of CuOTf, dtbpy (30 mol %), **1o** (0.4 mmol, 2.0 equiv), **6** (0.2 mmol, 1.0 equiv), DIPEA (4.0 equiv), DMSO (2 mL), rt, 10 W blue LEDs for 16 h, under N_2, isolated yield.

amines in the presence of 20 mol % of CuI, 30 mol % of bisoxazoline **L7**[14] and 4.0 equiv of DIPEA under irradiation of 10 W blue LEDs, gave the corresponding secondary and tertiary amines in moderate to good yields (For details, see the Supporting Information). The addition of nitrogen-based ligands might be stabilize the LUMOs of photoactive complexes and vary redox potentials and excited state lifetimes.[14d,e] The benzyl amine and 2-picolylamine reacted with **1o** smoothly to give the desired products **9a** and **9b** in 92%

and 60% yields, respectively (Scheme 5). Notably, primary aliphatic amines **8c-l** furnished the corresponding mono-cyanoalkylated products **9c-l** in 34-84% yields. Secondary

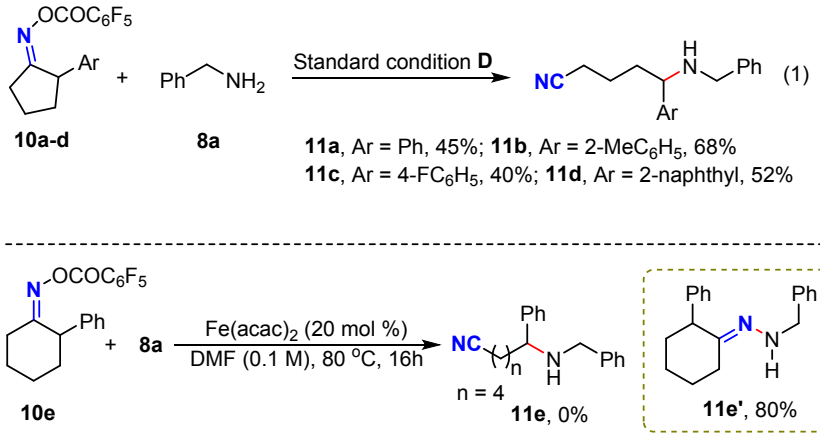
Scheme 5 Scope of Aliphatic Amines, Natural Products and Drugs[a]



[a]Standard condition **D**: 20 mol % of CuI, **L7** (30 mol %), **1o** (0.4 mmol, 2.0 equiv), **8** (0.2 mmol, 1.0 equiv), DIPEA (4.0 equiv), DMF (2 mL), rt, 10 W blue LEDs for 16 h, under N_2, isolated yield.

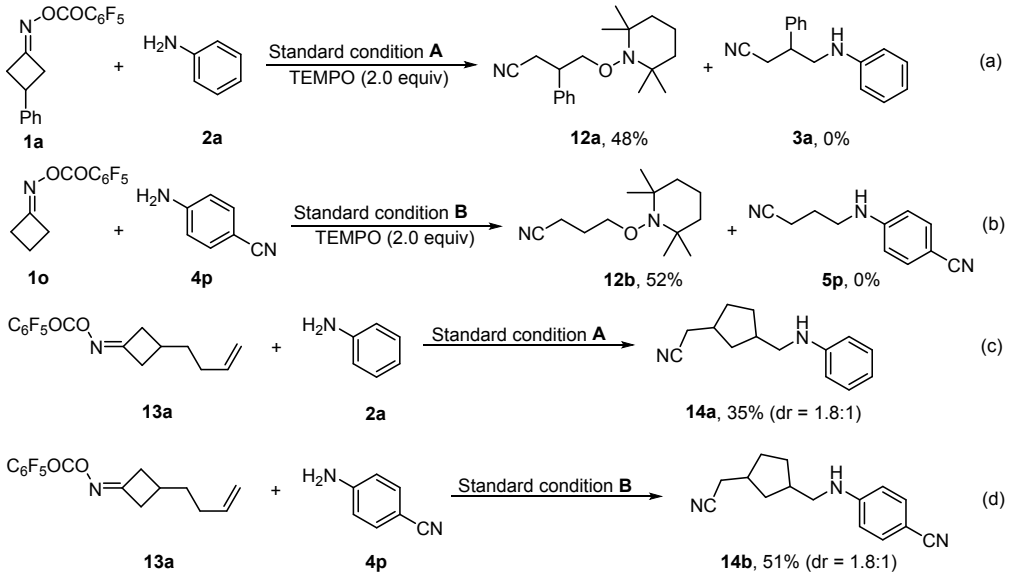
aliphatic amines, cyclic as well as acyclic, both gave the expected tertiary amines **9m-p** in 64-90% yields. Notably, with tryptamine **8f** and tryptophan methyl ester **8j**, the cyanoalkylation reactions occurred regioselectively, affording the products **9f** and **9j** in 71% and 34% yields, respectively. Finally, several natural products and drugs such as Leelamine, Memantine, Desloartadine and Amoxapine were also engaged in this cyanoalkylation reaction to afford the desired derivatives **9q-t** in satisfied yields, which clearly highlighted the potential utility of this protocol for late-stage modification of complex bioactive molecules. Satisfactorily, treatment of 2-phenylcyclopentanone oxime ester **1r** with benzyl amine **8a** furnished the secondary amine **9u** in 45% yield (eq 1). Satisfactorily, treatment of 2-substituted cyclopentanone oxime esters **10a-d** with benzyl amine **8a** furnished the secondary amine products **11a-d** in moderate yields (Scheme 6). Unfortunately, the use of 2-phenylcyclohexanone oxime in the reaction with **8a** failed to give the desired product **11e** under the standard condition **D**. We also attempt to improve the yield of **11e** by involving other catalysts, ligands and bases, but were unsuccessful (for details, see SI). While the ring-unopened product **11e'** was obtained in 80% yield when $Fe(acac)_2$ was used as a catalyst, due to the competitive direct coupling of oxime esters with amines.

Scheme 6 Scope of 2-Substituted Cyclopentanone and Cyclohexanone Oxime Esters



To elucidate the reaction mechanism, several control experiments were performed (Scheme 7). First, radical trapping experiments by adding a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to the reaction system were carried out. The addition of 2.0 equiv of TEMPO inhibited the amination reaction completely and yielded the TEMPO-adducts **12a** and **12b** in 48% and 52% yields, respectively (Scheme 7, a and b), indicating that these transformations involved radical intermediates. Furthermore, the radical clock substrate **13a** reacted with **2a** or **4p** furnishing the cyclization/amination product **14a** and **14b** in 35% and 51% yields, respectively (Scheme 7, c and d). These results were consistent with a possible radical pathway. Furthermore, a series of UV-Vis absorption spectra in Figure S1 showed that the mixture of amine **4p**, CuOTf and ligand **L3** exhibited a strong visible light absorption tailing to the 390-520 nm region. These observations suggest that a photo absorbing $L_nCu\text{-}NR^1R^2$ species might be involved in this transformation (for details, see the Supporting Information).[15] However, further mechanistic studies will be needed to gain thorough understanding of the reaction mechanism.[16]

Scheme 7 Mechanistic Investigation of the Cynoalkylation of Amines



CONCLUSIONS

In conclusion, we have developed a copper-catalyzed cyanoalkylation of amines via C−C bond cleavage. The reactions proceeded under very mild conditions (room temperature, free of exogenous photosensitizer) with exclusive selectivity and good functional group tolerance. Furthermore, a variety range of nitrogen nucleophiles including (hetero)aromatic amines, aromatic *N*-heterocycles, sulfonamides, and alkyl amines were amenable, thus providing a new and efficient approach to structurally diverse cyanoalkylated amines. Especially, this protocol is also applicable to late-stage functionalization of natural products, amino acid esters and drugs.

EXPERIMENTAL SECTION

General Methods. The reactions were conducted in oven-dried Schlenk-tube or the photoinduced reactions were carried out in reaction tubes with Wattecs blue LEDs (10 W, 460-470 nm) Irradiation Parallel Reactor under an atmosphere of nitrogen, the tube was placed 2 cm away from the Irradiation Parallel Reactor, water cooling was enforced for effective thermal management to maintain luminous efficiency and life expectancy of LED lights. Reactions were monitored by thin layer chromatography (TLC) and visualized using UV light or a basic $KMnO_4$ solution and heat. Column chromatography purifications were carried out using 200-300 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance III-400 in solvents as indicated. Chemical shift are reported in ppm from TMS with the solvent resonance as internal standard ($CDCl_3$: ^{1}H NMR: δ = 7.26; ^{13}C NMR: δ = 77.0; or DMSO-*d6*: ^{1}H NMR: δ = 2.50; ^{13}C NMR: δ = 39.52). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet),

t (triplet), q (quartet) and m (multiplet). FT-IR spectra were recorded on a Bruker V 70 spectrometer and only major peaks are reported in cm^{-1}. HRMS were obtained on a Q-TOF micro spectrometer. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification.

Note: if the amine, base or ligand is a liquid, its solution in solvent was used.

Starting Materials

All amines were purchased from commercial suppliers. All of cycloketone oxime esters **1** were synthesized from the corresponding cycloketones and carboxylic acids according to the literature.[11] The substituted cycloketones were prepared according to the reported procedure. [9, 10f, 17a] All of the NMR spectra of the know compounds were in full accordance with the data in the literatures.

Representative Procedure for the Reaction of Cyclobutanone Oxime Ester 1 with Aniline 2a-p, 4a-g and 4v-w (Method A)

A 10 mL oven-dried Schlenk-tube equipped with a magnetic stirrer was charged with cyclobutanone oxime ester **1** (0.2 mmol, 1.0 equiv), anilines **2a-p**, **4a-g**, **4v-w** (0.4 mmol, 2.0 equiv), and $Cu(OTf)_2$ (20 mol %). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, 1.0 mL of DMF and 1.0mL H_2O were added by syringe under nitrogen. The tube was then sealed and the mixture was stirred at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient eluent of petroleum ether/EtOAc/triethylamine: 100/20/3) to give the products **3a-p** in

Scheme 2, **5a-g**, **5v-w** in Scheme 3.

Representative Procedure for the Reaction of Cyclopentanone Oxime Esters 1q with Aniline 2a, Cyclobutanone Oxime Ester 1o with Aromatic Amines 4h-u, Heteroaromatic Amines and Aromatic *N*-Heterocycles 6a-c, 6e, **6m (Method B)**

A 10 mL oven-dried quartz reaction tube equipped with a magnetic stirrer was charged with cyclopentanone oxime esters **1q** (0.2 mmol, 1.0 equiv) with aniline **2a** (0.4 mmol, 2.0 equiv) or cyclobutanone oxime ester **1o** (0.2 mmol, 1.0 equiv) with aromatic amines **4h-u** (0.4 mmol, 2.0 equiv), heteroaromatic amines and aromatic *N*-heterocycles **6a-c**, **6e**, **6m** (0.4 mmol, 2.0 equiv), CuOTf (20 mol %), **L3** (10 mol %) and DIPEA (0.8 mmol, 4.0 equiv). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, 2.0 mL of DMF was added by syringe under nitrogen. The tube was then sealed and the reactions were stirred with Wattecs blue LEDs Irradiation Parallel Reactor at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the products **3q** in Scheme 2, **5h-u** in Scheme 3, **7a-c**, **7e** and **7m** in Scheme 4.

Representative Procedure for the Reaction of Cyclobutanone Oxime Ester 1o with Heteroaromatic Amines and Aromatic *N*-Heterocycles 6d, 6f-l (Method C)

A 10 mL oven-dried quartz reaction tube equipped with a magnetic stirrer was charged with cyclobutanone oxime ester **1o** (0.4 mmol, 2.0 equiv), heteroaromatic amines or aromatic *N*-heterocycles **6d**, **6f-l** (0.2 mmol, 1.0 equiv), CuOTf (20 mol %), dtbpy (30 mol %) and DIPEA (0.8 mmol, 4.0 equiv). Then, the tube was evacuated and backfilled with nitrogen for three times.

Subsequently, 2.0 mL of DMSO was added by syringe under nitrogen. The tube was then sealed and the reactions were stirred with Wattecs blue LEDs Irradiation Parallel Reactor at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the products **7d**, **7f-l** in Scheme 4.

Representative Procedure for the Reaction of Cyclobutanone Oxime Ester 1o with Aliphatic Amines 8 (Method D)

A 10 mL oven-dried quartz reaction tube equipped with a magnetic stirrer was charged with cyclobutanone oxime ester **1o** (0.4 mmol, 2.0 equiv), aliphatic amines **8** (0.2 mmol, 1.0 equiv), CuI (20 mol %), **L7** (30 mol %) and DIPEA (0.8 mmol, 4.0 equiv). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, 2.0 mL of DMF was added by syringe under nitrogen. The tube was then sealed and the reactions were stirred with Wattecs blue LEDs Irradiation Parallel Reactor at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the products **9** in Scheme 5.

Representative Procedure for the Reaction of 2-Substituted Cyclopentanone Oxime Ester 10a-d with Benzyl Amine 8a (Method D)

A 10 mL oven-dried quartz reaction tube equipped with a magnetic stirrer was charged with 2-substituted cyclopentanone oxime ester **10a-d** (0.4 mmol, 2.0 equiv), benzyl amine **8a** (0.2

mmol, 1.0 equiv), CuI (20 mol %), **L7** (30 mol %) and DIPEA (0.8 mmol, 4.0 equiv). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, 2.0 mL of DMF was added by syringe under nitrogen. The tube was then sealed and the reaction was stirred with Wattecs blue LEDs Irradiation Parallel Reactor at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the products **11a-d** in Scheme 6.

Representative Procedure for the Reaction of 2-Phenyl Cyclohexanone Oxime Ester 10e with Benzyl Amine 8a

A 10 mL oven-dried Schlenk-tube equipped with a magnetic stirrer was charged with 2-phenyl cyclohexanone oxime ester **10e** (0.4 mmol, 2.0 equiv), benzyl amine **8a** (0.2 mmol, 1.0 equiv), $Fe(acac)_2$ (20 mol %) and **L7** (30 mol %). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, 2.0 mL of DMF was added by syringe under nitrogen. The tube was then sealed and the mixture was stirred at 80 ^oC for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient eluent of petroleum ether/EtOAc/triethylamine: 100/20/3) to give the product **11e'** in Scheme 6.

Large Scale Procedure for the Synthesis of 3a: A 100 mL oven-dried Schlenk-tube equipped with a magnetic stirrer was charged with cyclobutanone oxime ester **1a** (1.07 g, 3.0 mmol, 1.0 equiv) and $Cu(OTf)_2$ (0.22 g, 20 mol %). Then, the tube was evacuated and backfilled with nitrogen for three times. Subsequently, aniline **2a** (0.56 g, 6.0 mmol, 2.0 equiv), 15.0 mL of DMF

and 15.0 mL H_2O were added by syringe under nitrogen. The tube was then sealed and the mixture was stirred at room temperature for 16 h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient eluent of petroleum ether/EtOAc/triethylamine: 100/20/3) to give the product **3a** (0.54 g, 76%), along with 65% of pentafluorobenzoic acid recovered.

Characterization of Products 3

3-Phenyl-4-(phenylamino)butanenitrile (3a): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (88%, 41.6 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.35 (m, 3H), 7.32 – 7.24 (m, 4H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 2H), 3.83 – 3.72 (t, *J* = 6.0 Hz, 1H), 3.64 – 3.54 (m, 1H), 3.49 – 3.43 (m, 1H), 3.36 – 3.30 (m, 1H), 2.81 – 2.68 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 147.1, 139.2, 129.2, 128.9, 127.7, 127.1, 118.2, 117.8, 112.8, 47.7, 41.1, 21.8 ppm; IR (neat): υ_{max} 3399, 2924, 2246, 1731, 1602, 1508, 1257, 752, 697 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}N_2$ $[M+H]^+$ 237.1386, found 237.1394.

4-(Phenylamino)-3-(*p*-tolyl)butanenitrile (3b): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (93%, 46.5 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.12 (m, 6H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 3.67 (s, 1H), 3.57 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.42 (dd, *J* = 12.9, 7.4 Hz, 1H), 3.33 – 3.26 (m, 1H), 2.82 – 2.64 (m, 2H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 147.2, 137.7, 136.2, 129.8, 129.3, 127.1, 118.3, 118.0, 113.0, 48.0, 40.9, 22.2, 21.0 ppm; IR (neat): υ_{max} 3399, 2922, 2246, 1602, 1510, 1321, 1259, 816, 751, 693 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543, found 251.1547.

3-(4-Butylphenyl)-4-(phenylamino)butanenitrile (3c): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (89%, 52.0 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.36 (m, 2H), 7.23 – 7.14 (m, 4H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.65 – 6.58 (m, 2H), 3.70 (s, 1H), 3.58 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.44 (dd, *J* = 13.0, 7.3 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.82 – 2.66 (m, 2H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 150.9, 147.2, 136.1, 129.3, 126.9, 126.0, 118.4, 118.0, 113.1, 48.0, 40.8, 34.5, 31.2, 22.2 ppm; IR (neat): υ_{max} 2962, 2246 , 1602, 1508, 1260, 800, 693 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}N_2$ $[M+H]^+$ 293.2012, found 293.2013.

3-(4-Chlorophenyl)-4-(phenylamino)butanenitrile (3d): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (71%, 38.4 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.35 (m, 2H), 7.22 – 7.18 (m, 4H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.60 (dd, *J* = 8.5, 0.9 Hz, 2H), 3.66 (s, 1H), 3.57 (dd, *J* = 12.9, 7.2 Hz, 1H), 3.42 (dd, *J* = 13.0, 7.3 Hz, 1H), 3.34 – 3.28 (m, 1H), 2.79 – 2.67 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 146.9, 137.7, 133.9, 129.4, 129.3, 128.7, 118.3, 117.9, 113.0, 47.9, 40.8, 22.1 ppm; IR (neat): υ_{max} 3399, 2924, 2247, 1602, 1493, 1259, 1093, 752, 694 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}ClN_2$ $[M+H]^+$ 271.0997, found 271.1003.

Methyl 4-(1-cyano-3-(phenylamino)propan-2-yl)benzoate (3e): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (60%, 35.3 mg); R_f 0.2 (EtOAc/petroleum ether = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 – 8.01 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.15 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.60 (dd, *J* = 8.5, 0.9 Hz, 2H), 3.93 (s, 3H), 3.63 (dd, *J* = 24.4, 8.0 Hz, 2H), 3.50 – 3.38 (m, 2H), 2.84 – 2.72 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 166.5, 146.9, 144.4, 130.4, 129.9, 129.4,

127.4, 118.3, 117.8, 113.0, 52.2, 47.9, 41.3, 21.8 ppm; IR (neat): υ_{max} 3397, 2959, 2247, 1719, 1603, 1283, 1110, 753, 695 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1441, found 295.1444.

4-(Phenylamino)-3-(m-tolyl)butanenitrile (3f): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (65%, 32.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.23 (m, 2H), 7.21 – 7.13 (m, 2H), 7.06 (s, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 2H), 3.77 – 3.51 (m, 2H), 3.43 (dd, *J* = 12.6, 7.5 Hz, 1H), 3.32 – 3.27 (m, 1H), 2.87 – 2.63 (m, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 147.2, 139.2, 138.9, 129.4, 129.0, 128.8, 128.0, 124.3, 118.1, 113.1, 99.6, 48.0, 41.3, 22.2, 21.4 ppm; IR (neat): υ_{max} 3396, 2921, 2246, 1602, 1507, 1260, 791, 694 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543, found 251.1548.

3-(3-Bromophenyl)-4-(phenylamino)butanenitrile (3g): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (58%, 36.5 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.42 (m, 1H), 7.39 (t, *J* = 1.7 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.16 (m, 3H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.60 (dd, *J* = 8.5, 0.9 Hz, 2H), 3.67 (s, 1H), 3.62 – 3.49 (m, 1H), 3.45 – 3.40 (m, 1H), 3.31 – 3.24 (m, 1H), 2.79 – 2.66 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 146.9, 141.6, 131.2, 130.7, 130.4, 129.4, 126.0, 123.2, 118.3, 117.8, 113.0, 47.9, 41.1, 21.9 ppm; IR (neat): υ_{max} 3397, 2923, 2246, 1602, 1567, 1259, 1074, 788, 694 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}BrN_2$ $[M+H]^+$ 315.0491, found 315.0494.

3-(2,3-Dichlorophenyl)-4-(phenylamino)butanenitrile (3h): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid

(55%, 33.4 mg); R_f 0.21 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.42 (m, 1H), 7.26 (dd, *J* = 7.1, 4.0 Hz, 2H), 7.23 – 7.15 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.63 (dd, *J* = 8.6, 0.9 Hz, 2H), 4.03 – 3.89 (m, 1H), 3.75 (s, 1H), 3.56 (d, *J* = 6.6 Hz, 2H), 2.90 – 2.74 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 146.9, 138.9, 134.0, 132.5, 129.9, 129.4, 127.8, 125.7, 118.3, 117.6, 112.9, 46.5, 38.1, 20.7 ppm; IR (neat): υ_{max} 3399, 2925, 2248, 1600, 1507, 1260, 792, 693 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}Cl_2N_2$ $[M+H]^+$ 305.0607, found 305.0608.

3-Benzyl-4-(phenylamino)butanenitrile (3i): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (93%, 46.5 mg); R_f 0.35 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.12 (m, 5H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 2H), 3.79 (s, 1H), 3.32 – 3.17 (m, 2H), 2.87 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.72 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.39 – 2.27 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 147.4, 138.1, 129.3, 128.9, 128.7, 126.8, 118.2, 117.9, 112.8, 46.7, 37.7, 37.2, 19.4 ppm; IR (neat): υ_{max} 3404, 2974, 2246, 1602, 1497, 1048, 747, 694 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543, found 251.1537.

5-Cyano-4-((phenylamino)methyl)pentyl benzoate (3j): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (60%, 38.7 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 2H), 4.37 (t, *J* = 6.4 Hz, 2H), 3.80 (s, 1H), 3.30 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.17 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.65 – 2.42 (m, 2H), 2.22 – 2.08 (m, 1H), 1.99 – 1.78 (m, 2H), 1.77 – 1.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 166.5, 147.4, 133.0, 130.0, 129.5, 129.4, 128.4, 118.1, 118.0, 112.8, 64.3, 46.9, 35.0, 28.0, 26.0, 19.9 ppm; IR (neat): υ_{max}

3400, 2925, 2245, 1716, 1602, 1509, 1274, 1114, 713, 694 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ 323.1754, found 323.1757.

3-(Benzyloxy)-4-(phenylamino)butanenitrile (3k): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (52%, 27.7 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.28 (m, 5H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 4.67 (dd, *J* = 39.3, 11.6 Hz, 2H), 4.03 – 3.83 (m, 2H), 3.48 – 3.21 (m, 2H), 2.68 (d, *J* = 5.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.3, 137.0, 129.3, 128.6, 128.2, 127.9, 118.2, 117.2, 113.1, 73.0, 72.3, 46.3, 21.2 ppm; IR (neat): υ_{max} 3398, 2925, 2249, 1603, 1508, 1260, 1097, 750, 695 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1492, found 267.1500.

3-Methyl-3-phenyl-4-(phenylamino)butanenitrile (3l): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (87%, 43.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.29 (m, 5H), 7.20 – 7.10 (m, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.60 – 6.54 (m, 2H), 3.46 (dd, *J* = 36.6, 12.5 Hz, 2H), 3.29 (s, 1H), 2.85 (s, 2H), 1.63 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.8, 142.0, 129.3, 129.1, 127.5, 125.8, 118.1, 117.9, 113.2, 53.5, 41.5, 28.4, 24.3 ppm; IR (neat): υ_{max} 3394, 2964, 2244, 1602, 1501, 1258, 1029, 799, 752, 696 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543, found 251.1546.

***tert*-Butyl 4-(cyanomethyl)-4-((phenylamino)methyl)piperidine-1-carboxylate (3m):** Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (79%, 52.0 mg); R_f 0.2 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 – 7.14 (m, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.71 – 6.65 (m, 2H),

3.64 (d, *J* = 13.2 Hz, 3H), 3.26 (dt, *J* = 19.1, 6.2 Hz, 4H), 2.53 (s, 2H), 1.66 – 1.59 (m, 4H), 1.46 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 154.6, 148.0, 129.4, 118.3, 117.5, 113.2, 79.9, 50.5, 36.3, 32.2, 28.3, 23.7 ppm; IR (neat): υ_{max} 3378, 2929, 2244, 1686, 1602, 1424, 1261, 1157, 750, 694 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{28}N_3O_2$ $[M+H]^+$ 330.2176, found 330.2180.

2-(3-Phenyl-1-((phenylamino)methyl)cyclobutyl)acetonitrile (3n): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (86%, 47.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); the title compound as a 1:1 mixture of inseparable diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (q, *J* = 7.1 Hz, 2H), 7.27 – 7.13 (m, 5H), 6.79 – 6.68 (m, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.60 (tq, *J* = 18.3, 9.2 Hz, 2H), 3.46 (s, 1H), 3.27 (s, 1H), 2.76 (s, 1H), 2.59 (s, 1H), 2.50 – 2.35 (m, 2H), 2.29 – 2.18 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 148.1, 148.0, 144.2, 144.1, 129.4, 129.3, 128.5, 128.4, 126.4, 126.3, 126.2, 126.2, 118.4, 118.2, 118.1, 118.0, 113.1, 113.1, 52.2, 50.0, 37.4, 36.7, 36.5, 36.5, 33.2, 32.9, 27.3, 25.4 ppm; IR (neat): υ_{max} 3393, 2928, 2244, 1602, 1509, 1257, 752, 696 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}N_2$ $[M+H]^+$ 277.1699, found 277.1703.

4-(Phenylamino)butanenitrile (3o): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (80%, 25.6 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 2H), 3.64 (s, 1H), 3.32 (t, *J* = 6.6 Hz, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 2.00 – 1.94 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.4, 129.3, 119.3, 117.9, 112.8, 42.2, 25.2, 14.7 ppm. Spectral data match those previously reported.[17b]

(*E*)-3,5-Diphenylpent-4-enenitrile (3p'): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (88%, 41.0 mg);

R_f 0.28 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.36 (m, 4H), 7.35 – 7.26 (m, 6H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.40 (dd, *J* = 15.9, 7.3 Hz, 1H), 3.89 (q, *J* = 7.2 Hz, 1H), 2.92 – 2.77 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 140.5, 136.3, 131.9, 129.2, 129.0, 128.5, 127.8, 127.6, 127.2, 126.4, 118.1, 44.9, 24.4 ppm; IR (neat): υ_{max} 3027, 2961, 2245, 1599, 1493, 1452, 1260, 1028, 965, 745, 696 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}N$ $[M+H]^+$ 234.1277, found 234.1282.

2-(3-(Phenylamino)cyclopentyl)acetonitrile (3q): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (28%, 11.2 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); the title compound as a 1:1 mixture of inseparable diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.13 (m, 2H), 6.73 – 6.69 (m, 1H), 6.65 – 6.55 (m, 2H), 4.01 – 3.80 (m, 1H), 3.67 (s, 1H), 3.15 (d, *J* = 6.8 Hz, 0.7H), 2.89 – 2.66 (m, 0.3H), 2.48 – 2.38 (m, 2H), 2.34 – 2.25 (m, 1H), 2.11 – 1.90 (m, 2H), 1.79 – 1.41 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 147.9, 147.5, 147.3, 129.2, 129.2, 122.9, 118.8, 118.8, 117.5, 117.4, 113.2, 113.1, 112.7, 54.2, 53.8, 48.5, 39.8, 39.2, 39.1, 35.6, 34.9, 34.5, 33.5, 32.9, 30.5, 30.4, 29.9, 29.5, 27.5, 23.0, 22.6 ppm; IR (neat): υ_{max} 3394, 2973, 2242, 1602, 1501, 1048, 749, 693 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{20}N_3$ $[M+NH_4]^+$ 218.1652, found 218.1647.

Characterization of Products 5

4-(*o*-Tolylamino)butanenitrile (5a): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (88%, 30.6 mg); R_f 0.2 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 3.56 (s, 1H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.15 (s, 3H), 2.05 – 1.98 (m, 2H); ^{13}C{^{1}H} NMR

(101 MHz, $CDCl_3$): δ = 145.3, 130.3, 127.1, 122.2, 119.4, 117.4, 109.5, 42.2, 25.1, 17.4, 14.8 ppm; IR (neat): υ_{max} 3433, 2962, 2245, 1604, 1511, 1260, 1021, 799, 702 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}KN_2$ $[M+K]^+$ 213.0789, found 213.0785.

4-((2-Methoxyphenyl)amino)butanenitrile (5b): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (89%, 33.8 mg); R_f 0.17 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.70 (t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 4.26 (s, 1H), 3.85 (s, 3H), 3.33 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.03 – 1.96 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.8, 137.4, 121.2, 119.3, 117.0, 109.7, 109.6, 55.4, 42.0, 25.3, 14.8 ppm. Spectral data match those previously reported.[17c]

4-(*m*-Tolylamino)butanenitrile (5c): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (60%, 20.9 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 8.3, 7.5 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 7.4 Hz, 2H), 3.65 (s, 1H), 3.31 (t, *J* = 6.6 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 2.00 – 1.93 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.5, 139.2, 129.2, 119.3, 118.8, 113.6, 109.9, 42.2, 25.2, 21.5, 14.7 ppm; IR (neat): υ_{max} 2962, 2245, 1416, 1260, 1092, 1020, 799, 691 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2$ $[M+H]^+$ 175.1230, found 175.1235.

4-((3-Methoxyphenyl)amino)butanenitrile (5d): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (31%, 11.8 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.09 (t, *J* = 8.1 Hz, 1H), 6.46 – 6.19 (m, 2H), 6.17 (t, *J* = 2.3 Hz, 1H), 3.76 (d, *J* =

10.3 Hz, 4H), 3.30 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 1.99 – 1.92 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 160.8, 148.8, 130.1, 119.3, 105.9, 102.8, 98.8, 55.0, 42.2, 25.1, 14.7 ppm; IR (neat): υ_{max} 2962, 2245, 1597, 1261, 1094, 1023, 799, 687 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.1179, found 191.1186.

4-(*p*-Tolylamino)butanenitrile (5e): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (82%, 28.6 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 8.3 Hz, 2H), 3.54 (s, 1H), 3.26 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.22 (s, 3H), 1.96 – 1.89 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 145.1, 129.8, 127.1, 119.3, 112.9, 42.5, 25.2, 20.3, 14.7 ppm; IR (neat): υ_{max} 2961, 2245, 1518, 1260, 1093, 1019, 800, 704 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2$ $[M+H]^+$ 175.1230, found 175.1236.

4-((4-Methoxyphenyl)amino)butanenitrile (5f): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (65%, 24.7 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 – 6.78 (m, 2H), 6.64 – 6.44 (m, 2H), 3.75 (s, 3H), 3.41 (s, 1H), 3.26 (dd, *J* = 8.8, 4.3 Hz, 2H), 2.47 (dd, *J* = 9.5, 4.5 Hz, 2H), 2.11 – 1.80 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 152.4, 141.6, 119.4, 114.9, 114.2, 55.7, 43.2, 25.3, 14.8 ppm; IR (neat): υ_{max} 3393, 2961, 2245, 1512, 1260, 1094, 1025, 799, 704 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.1179, found 191.1188.

4-((2,4-Dimethoxyphenyl)amino)butanenitrile (5g): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (48%, 21.1 mg); R_f 0.12 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 6.54 – 6.40 (m, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.27 (t, *J* = 6.6 Hz, 2H), 2.85 (s, 1H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.01 – 1.94 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 152.2, 148.0, 131.6, 119.4, 110.3, 103.7, 99.2, 55.7, 55.4, 42.8, 25.4, 14.8 ppm; IR (neat): υ_{max} 2962, 2245, 1517, 1260, 1093, 1020, 799 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_2O_2$ $[M+H]^+$ 221.1285, found 221.1288.

4-((2-Fluorophenyl)amino)butanenitrile (5h): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (65%, 23.2 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 – 6.93 (m, 2H), 6.73 – 6.63 (m, 2H), 3.94 (s, 1H), 3.35 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.03 – 1.96 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.5 (d, *J* = 237.0 Hz), 136.4 (d, *J* = 11.4 Hz), 124.6 (d, *J* = 3.4 Hz), 119.1, 117.2 (d, *J* = 6.9 Hz), 114.6 (d, *J* = 18.3 Hz), 111.9 (d, *J* = 3.0 Hz), 41.9, 25.2, 14.7 ppm; IR (neat): υ_{max} 3395, 2962, 2246, 1620, 1512, 1260, 1091, 1020, 798 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}FN_3$ $[M+NH_4]^+$ 196.1245, found 196.1238.

4-((2-Bromophenyl)amino)butanenitrile (5i): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (52%, 24.8 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.23 – 7.14 (m, 1H), 6.69 – 6.55 (m, 2H), 4.34 (s, 1H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.05 – 1.98 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.2, 132.6, 128.5, 119.1, 118.3, 111.1, 109.9, 42.1, 25.0, 14.7 ppm; IR (neat): υ_{max} 3398, 2961, 2246, 1737, 1595, 1260, 1094, 1018, 799 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}BrN_2$ $[M+H]^+$ 239.0178, found 239.0186.

4-([1,1'-Biphenyl]-2-ylamino)butanenitrile (5j): Following the Method B with the

corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (80%, 37.8 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 – 7.43 (m, 2H), 7.43 – 7.34 (m, 3H), 7.30 – 7.21 (m, 1H), 7.11 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.81 (td, *J* = 7.4, 0.9 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 1H), 3.29 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.95 – 1.88 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.2, 139.1, 130.4, 129.2, 128.9, 128.7, 128.0, 127.3, 119.2, 117.5, 110.3, 42.3, 25.1, 14.7 ppm; IR (neat): υ_{max} 3419, 2962, 2246, 1580, 1262, 1086, 800, 703 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}N_3$ $[M+NH_4]^+$ 254.1652, found 254.1651.

4-((3-Chlorophenyl)amino)butanenitrile (5k): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (75%, 29.1 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (t, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.58 (s, 1H), 6.48 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.81 (s, 1H), 3.30 (d, *J* = 4.1 Hz, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.00 – 1.93 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 148.6, 135.1, 130.3, 119.1, 117.7, 112.4, 111.1, 42.1, 24.9, 14.7 ppm; IR (neat): υ_{max} 2962, 2244, 1601, 1511, 1260, 1093, 1023, 799 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}ClN_2$ $[M+H]^+$ 195.0684, found 195.0691.

4-((4-Fluorophenyl)amino)butanenitrile (5l): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (78%, 27.8 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 – 6.78 (m, 2H), 6.66 – 6.41 (m, 2H), 3.61 (s, 1H), 3.28 (t, *J* = 6.5 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.00 – 1.93 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 156.0 (d, *J* = 234.2 Hz), 143.8, 119.3, 115.7 (d, *J* = 22.2 Hz), 113.7 (d, *J* = 7.3 Hz), 42.9, 25.1, 14.7 ppm; IR (neat): υ_{max} 2962, 2246, 1510,

1260, 1091, 1019, 799, 701 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}FN_2$ $[M+H]^+$ 179.0979, found 179.0987.

4-((4-Chlorophenyl)amino)butanenitrile (5m): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (82%, 31.8 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 – 6.95 (m, 2H), 6.57 – 6.45 (m, 2H), 3.74 (s, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.98 – 1.91 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.0, 129.1, 122.4, 119.2, 113.8, 42.3, 25.0, 14.7 ppm; IR (neat): υ_{max} 2962, 2246, 1260, 1090, 1019, 799, 700 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}ClN_2$ $[M+H]^+$ 195.0684, found 195.0690.

4-((4-Bromophenyl)amino)butanenitrile (5n): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (60%, 28.6 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.23 (m, 2H), 6.55 – 6.36 (m, 2H), 3.74 (s, 1H), 3.29 (t, *J* = 6.6 Hz, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 1.99 – 1.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.4, 132.0, 119.1, 114.3, 109.5, 42.3, 25.0, 14.8 ppm; IR (neat): υ_{max} 2962, 2246, 1260, 1092, 1019, 799, 696 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}BrN_2$ $[M+H]^+$ 239.0178, found 239.0180.

4-((4-Iodophenyl)amino)butanenitrile (5o): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (61%, 34.9 mg); R_f 0.2 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.34 (m, 2H), 6.40 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 1H), 3.29 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.98 – 1.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.0, 137.9, 119.1, 115.0, 78.5, 42.1, 24.9, 14.7 ppm; IR (neat): υ_{max} 2962, 2245, 1260, 1019, 799, 701 cm^{-1}; HRMS (ESI) calcd for

$C_{10}H_{12}IN_2$ $[M+H]^+$ 287.0040, found 287.0043.

4-((3-Cyanopropyl)amino)benzonitrile (5p): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (78%, 28.9 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.53 (s, 1H), 3.35 (q, *J* = 6.5 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.02 – 1.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 150.7, 133.7, 120.2, 119.0, 112.1, 98.9, 41.4, 24.6, 14.7 ppm; IR (neat): υ_{max} 3373, 2936, 2247, 2211, 1607, 1527, 1341, 1174, 825, 688 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}N_3$ $[M+H]^+$ 186.1026, found 186.1029.

4-((4-(Trifluoromethyl)phenyl)amino)butanenitrile (5q): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (51%, 23.3 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.09 (s, 1H), 3.36 (q, *J* = 6.4 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.02 – 1.95 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 149.9, 126.8 – 126.6 (m, 3C), 123.7 (q, *J* = 273.2 Hz), 119.3, 111.9, 41.8, 24.9, 14.7 ppm; IR (neat): υ_{max} 2962, 2248, 1619, 1260, 1094, 1020, 799, 703 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}F_3N_2$ $[M+H]^+$ 229.0947, found 229.0950.

4-((4-(Methylsulfonyl)phenyl)amino)butanenitrile (5r): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (40%, 19.0 mg); R_f 0.11 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.62 (t, *J* = 5.6 Hz, 1H), 3.35 (q, *J* = 6.5 Hz, 2H), 2.99 (s, 3H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.01 – 1.94 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.7, 129.3, 127.6, 119.0, 111.8, 44.9, 41.5, 24.6, 14.7 ppm; IR (neat): υ_{max}

3368, 2962, 2245, 1596, 1261, 1132, 1088, 801, 766 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2O_2S$ $[M+H]^+$ 239.0849, found 239.0848.

4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)butanenitrile (5s): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (53%, 30.3 mg); R_f 0.12 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.5 Hz, 2H), 6.59 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 1H), 3.35 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.00 – 1.93 (m, 2H), 1.32 (s, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 149.9, 136.4, 119.2, 111.8, 99.9, 83.2, 41.7, 25.0, 24.8, 14.7 ppm; IR (neat): υ_{max} 2962, 2246, 1605, 1260, 1086, 1019, 799, 657 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}BN_2O_2$ $[M+H]^+$ 287.1925, found 287.1927.

4-((4-Fluoro-2-methylphenyl)amino)butanenitrile (5t): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (52%, 20.0 mg); R_f 0.21 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 – 6.73 (m, 2H), 6.51 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.32 (t, *J* = 6.7 Hz, 3H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.14 (s, 3H), 2.05 – 1.95 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 155.6 (d, *J* = 233.7 Hz), 141.6, 124.1 (d, *J* = 7.1 Hz), 119.3, 117.1 (d, *J* = 22.3 Hz), 112.8 (d, *J* = 21.5 Hz), 110.2 (d, *J* = 7.7 Hz), 42.7, 25.1, 17.5, 14.9 ppm; IR (neat): υ_{max} 2962, 2246, 1511, 1261, 1021, 799, 707 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}FN_2$ $[M+H]^+$ 193.1136, found 193.1141.

4-(Naphthalen-1-ylamino)butanenitrile (5u): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (42%, 17.6 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 – 7.79 (m, 2H), 7.50 – 7.42 (m, 2H), 7.39 – 7.33 (m, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 7.4 Hz,

1H), 4.39 (s, 1H), 3.51 (s, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.16 – 2.10 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 142.6, 134.3, 128.7, 126.4, 125.8, 124.9, 123.5, 119.6, 119.4, 118.1, 104.5, 42.5, 24.9, 15.0 ppm; IR (neat): υ_{max} 2962, 2244, 1511, 1409, 1260, 1019, 799, 704 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}N_2Na$ $[M+Na]^+$ 233.1049, found 233.1044.

4-(Methyl(phenyl)amino)butanenitrile (5v): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic aniline (0.4 mmol). Faint yellow liquid (57%, 19.8 mg); R_f 0.29 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.20 (m, 2H), 6.74 (t, *J* = 7.6 Hz, 3H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.96 (s, 3H), 2.40 (t, *J* = 7.0 Hz, 2H), 1.99 – 1.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 148.9, 129.3, 119.3, 117.0, 112.5, 51.2, 38.7, 23.1, 14.7 ppm; IR (neat): υ_{max} 2961, 2924, 2244, 1597, 1501, 1260, 1020, 799, 690 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}N_2$ $[M+H]^+$ 175.1230, found 175.1237.

Ethyl *N*-(3-Cyanopropyl)-*N*-phenylglycinate (5w): Following the Method A with the corresponding cyclobutanone oxime ester (0.2 mmol) and aniline (0.4 mmol). Faint yellow liquid (46%, 22.6 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 8.7, 7.4 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 3.57 (t, *J* = 6.9 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.05 – 1.98 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 170.9, 147.3, 129.4, 119.4, 117.9, 112.6, 61.1, 54.0, 50.4, 23.7, 14.6, 14.1 ppm; IR (neat): υ_{max} 2982, 2243, 1746, 1598, 1504, 1245, 1194, 748, 691 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 247.1441, found 247.1442.

Characterization of Products 7

4-(Pyridin-2-ylamino)butanenitrile (7a): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and heteroaromatic amine (0.4 mmol). Faint yellow liquid

(32%, 10.3 mg); R_f 0.12 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 – 8.04 (m, 1H), 7.44 – 7.39 (m, 1H), 6.61 – 6.58 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 4.58 (s, 1H), 3.48 (q, *J* = 6.5 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.03 – 1.96 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.2, 148.0, 137.4, 119.4, 113.3, 107.3, 40.4, 25.5, 14.7 ppm; IR (neat): υ_{max} 3390, 2928, 2245, 1769, 1521, 1379, 819, 792 cm^{-1}; HRMS (ESI) calcd for $C_9H_{12}N_3$ $[M+H]^+$ 162.1026, found 162.1033.

4-(Quinolin-8-ylamino)butanenitrile (7b): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and heteroaromatic amine (0.4 mmol). Faint yellow liquid (58%, 24.5 mg); R_f 0.14 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.49 – 7.30 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.21 (s, 1H), 3.52 (q, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.15 – 2.08 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.9, 144.1, 138.1, 136.0, 128.6, 127.6, 121.5, 119.3, 114.5, 104.7, 41.7, 25.1, 14.9 ppm; IR (neat): υ_{max} 3393, 2961, 2925, 2245, 1601, 1511, 1260, 1090, 1090, 799, 735 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}N_3$ $[M+H]^+$ 212.1182, found 212.1188.

4-(Benzo[*d*]thiazol-6-ylamino)butanenitrile (7c): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and heteroaromatic amine (0.4 mmol). Faint yellow liquid (40%, 17.4 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.98 (s, 1H), 3.38 (d, *J* = 4.6 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.05 – 1.98 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 149.4, 146.2, 145.8, 135.8, 123.9, 119.1, 114.7, 102.1, 42.5, 24.9, 14.8 ppm; IR (neat): υ_{max} 3384, 2962, 2245, 1758, 1604, 1484, 1246, 820, 731 cm^{-1};

HRMS (ESI) calcd for $C_{11}H_{12}N_3S$ $[M+H]^+$ 218.0746, found 218.0752.

4-(3-Acetyl-1*H*-indol-1-yl)butanenitrile (7d): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (72%, 32.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.47 – 8.30 (m, 1H), 7.77 (s, 1H), 7.43 – 7.29 (m, 3H), 4.38 (t, *J* = 6.4 Hz, 2H), 2.55 (s, 3H), 2.36 – 2.24 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 192.9, 136.4, 134.3, 126.4, 123.7, 123.0, 122.9, 118.2, 117.7, 109.3, 45.0, 27.7, 25.5, 14.6 ppm; IR (neat): υ_{max} 2962, 2246, 1639, 1460, 1261, 1019, 799 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1179, found 227.1183.

4-(9*H*-Carbazol-9-yl)butanenitrile (7e): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic *N*-heterocycle (0.4 mmol). Faint yellow liquid (34%, 15.9 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.8 Hz, 2H), 7.52 – 7.43 (m, 4H), 7.29 – 7.25 (m, 1.6H), 7.25 (d, *J* = 1.1 Hz, 0.4H), 4.50 (t, *J* = 6.2 Hz, 2H), 2.38 – 2.24 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 140.1, 126.0, 123.0, 120.5, 119.4, 119.1, 108.3, 41.0, 25.0, 15.0 ppm; IR (neat): υ_{max} 2960, 2252, 1722, 1646, 1260, 1092, 1024, 802, 696 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2$ $[M+H]^+$ 235.1230, found 235.1231.

4-(10*H*-Phenothiazin-10-yl)butanenitrile (7f): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (33%, 17.6 mg); R_f 0.25 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, *J* = 11.8, 4.5 Hz, 4H), 7.00 – 6.93 (m, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.19 – 2.09 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.7, 127.8, 127.4, 126.2, 123.0, 119.3, 115.6, 45.2, 22.9, 14.3 ppm. IR (neat): υ_{max} 3395, 2975, 2249,

1652, 1456, 1048, 880, 752 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_2S$ $[M+H]^+$ 267.0950, found 267.0946.

4-(1*H*-Benzo[d]imidazol-1-yl)butanenitrile (7g): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (62%, 22.9 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.90 (dd, *J* = 6.4, 2.7 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.26 (dd, *J* = 6.2, 2.7 Hz, 1H), 4.57 (t, *J* = 5.9 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.25 – 2.12 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.1, 141.8, 132.8, 124.7, 123.8, 120.9, 118.2, 110.4, 64.4, 24.5, 14.1 ppm; IR (neat): υ_{max} 3397, 2974, 2252, 1739, 1493, 1277, 1231, 1049, 881, 747 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}N_3$ $[M+H]^+$ 186.1026, found 186.1025.

4-(2-Chloro-1H-benzo[d]imidazol-1-yl)butanenitrile (7h): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic N-heterocycle (0.2 mmol). Faint yellow liquid (44%, 19.3 mg); R_f 0.2 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.67 (m, 1H), 7.44 – 7.27 (m, 3H), 4.37 (t, *J* = 6.8 Hz, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.26 – 2.20 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 141.7, 140.1, 134.8, 123.7, 123.1, 119.8, 118.2, 108.9, 42.4, 25.4, 14.7 ppm; IR (neat): υ_{max} 2961, 2926, 2247, 1729, 1470, 1261, 1023, 799, 743 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}ClN_3$ $[M+H]^+$ 220.0636, found 220.0636.

4-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9*H*-purin-9-yl)butanenitrile (7i): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (45%, 22.2 mg); R_f 0.15 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 4.55 (t, *J* = 5.9 Hz, 2H), 3.67 (s, 3H), 3.38 (s, 3H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.22 – 2.12 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 155.1,

151.5, 149.3, 141.2, 118.0, 106.7, 45.5, 29.8, 28.0, 26.3, 14.3 ppm; IR (neat): υ_{max} 3447, 2971, 2249, 1738, 1658, 1491, 1242, 1036, 995, 748 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}N_5NaO_2$ $[M+Na]^+$ 270.0961, found 270.0956.

4-(4-Bromo-1*H*-pyrazol-1-yl)butanenitrile (7j): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (40%, 17.0 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 – 7.77 (m, 2H), 4.55 (t, *J* = 5.9 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.23 – 2.12 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.6, 131.8, 118.3, 96.9, 64.3, 24.6, 14.1 ppm; IR (neat): υ_{max} 2961, 2249, 1737, 1491, 1259, 1022, 800 cm^{-1}; HRMS (ESI) calcd for $C_7H_9BrN_3$ $[M+H]^+$ 213.9974, found 213.9983.

4-(3-Chloro-1*H*-indazol-1-yl)butanenitrile (7k): Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (79%, 34.6 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.23 (d, *J* = 6.9 Hz, 1H), 4.47 (t, *J* = 6.0 Hz, 2H), 2.43 – 2.26 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 141.1, 133.8, 128.0, 121.6, 121.1, 119.9, 118.7, 108.9, 46.7, 25.5, 14.7 ppm; IR (neat): υ_{max} 2962, 2246, 1758, 1245, 1054, 799, 739 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}ClN_3$ $[M+H]^+$ 220.0636, found 220.0643.

***N*-(3-Cyanopropyl)benzenesulfonamide (7l):** Following the Method C with the corresponding cyclobutanone oxime ester (0.4 mmol) and aromatic *N*-heterocycle (0.2 mmol). Faint yellow liquid (37%, 16.5 mg); R_f 0.2 (EtOAc/petroleum ether = 1: 3); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 – 7.80 (m, 2H), 7.66 – 7.59 (m, 1H), 7.59 – 7.50 (m, 2H), 4.85 (t, *J* = 6.1 Hz, 1H), 3.09 (q, *J* = 6.5 Hz, 2H), 2.45 (t, *J* = 7.1 Hz, 2H), 1.91 – 1.84 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ

= 139.4, 133.0, 129.3, 126.9, 118.8, 41.5, 25.7, 14.3 ppm; IR (neat): υ_{max} 2962, 2248, 1416, 1260, 1091, 1020, 799, 688 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}N_2O_2S$ $[M+H]^+$ 225.0692, found 225.0696.

4-Amino-*N*-(3-cyanopropyl)-*N*-(pyrimidin-2-yl)benzenesulfonamide (7m): Following the Method B with the corresponding cyclobutanone oxime ester (0.2 mmol) and aromatic *N*-heterocycle (0.4 mmol). Faint yellow liquid (30%, 19.0 mg); R_f 0.12 (EtOAc/petroleum ether = 1: 3); ^1H NMR (400 MHz, DMSO-*d6*): δ = 8.57 (s, 1H), 8.56 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.08 (t, *J* = 4.8 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.11 (s, 2H), 4.24 – 4.07 (m, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.06 – 1.96 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-*d6*): δ = 157.8, 157.7, 153.3, 130.4, 124.2, 120.0, 115.7, 111.9, 99.4, 45.5, 25.0, 13.8 ppm; IR (neat): υ_{max} 3442, 2250, 2124, 1658, 1412, 1028, 823, 761, 626 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}N_5O_2S$ $[M+H]^+$ 318.1019, found 318.1012.

Characterization of Products 9

4-(Benzylamino)butanenitrile (9a): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (92%, 32.0 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.30 (m, 5H), 4.65 (d, *J* = 6.1 Hz, 2H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.42 (dd, *J* = 7.7, 4.0 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.14 – 2.07 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.0, 128.9, 128.0, 127.4, 118.7, 62.9, 49.2, 24.7, 14.1 ppm. Spectral data match those previously reported.[17d]

4-((Pyridin-2-ylmethyl)amino)butanenitrile (9b): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (60%, 21.0 mg); R_f 0.13 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz,

$CDCl_3$): δ = 8.59 (d, *J* = 4.7 Hz, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 7.25 (dd, *J* = 12.2, 5.7 Hz, 2H), 6.03 (s, 1H), 4.85 – 4.70 (m, 2H), 4.42 (t, *J* = 5.8 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.16 – 2.05 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 155.5, 149.0, 136.8, 122.6, 121.6, 118.7, 62.8, 48.8, 24.8, 14.1 ppm; IR (neat): υ_{max} 3343, 2962, 2249, 1722, 1650, 1545, 1499, 1305, 1233, 799, 759 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}N_3Na$ $[M+Na]^+$ 198.1002, found 198.1010.

4-(Butylamino)butanenitrile (9c): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (84%, 23.5 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.42 (t, *J* = 5.8 Hz, 2H), 4.22 (s, 1H), 3.48 (dd, *J* = 13.6, 6.9 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.18 – 2.02 (m, 2H), 1.62 (dd, *J* = 14.9, 7.5 Hz, 2H), 1.48 – 1.35 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 118.7, 62.8, 45.0, 32.8, 24.8, 19.7, 14.1, 13.6 ppm; IR (neat): υ_{max} 3368, 2962, 2250, 1719, 1645, 1499, 1305, 1211, 1027, 799 cm^{-1}; HRMS (ESI) calcd for $C_8H_{16}KN_2$ $[M+K]^+$ 179.0945, found 179.0937.

4-((3-Phenylpropyl)amino)butanenitrile (9d): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (70%, 28.3 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.4 Hz, 2H), 7.20 (dd, *J* = 15.7, 7.3 Hz, 3H), 4.42 (t, *J* = 5.8 Hz, 2H), 4.23 (s, 1H), 3.51 (dd, *J* = 13.8, 6.7 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.18 – 2.04 (m, 2H), 2.03 – 1.90 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 140.7, 128.5, 128.2, 126.2, 118.7, 62.8, 44.7, 32.8, 32.1, 24.8, 14.1 ppm; IR (neat): υ_{max} 3376, 2961, 2250, 1721, 1647, 1499, 1305, 1260, 1030, 800, 700 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}N_2Na$ $[M+Na]^+$ 225.1362, found 225.1372.

4-((2-(Thiophen-2-yl)ethyl)amino)butanenitrile (9e): Following the Method D with the

corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (77%, 30.2 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (dd, *J* = 5.1, 0.9 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.85 (d, *J* = 2.9 Hz, 1H), 4.42 (t, *J* = 5.8 Hz, 3H), 3.76 (q, *J* = 6.6 Hz, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.18 – 2.03 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 139.9, 127.1, 125.7, 124.3, 118.7, 62.9, 46.4, 30.9, 24.7, 14.1 ppm; IR (neat): υ_{max} 3368, 2961, 2924, 2250, 1718, 1640, 1260, 1091, 1021, 799, 695 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}N_2S$ $[M+H]^+$ 195.0950, found 195.0951.

4-((2-(1*H*-indol-3-yl)ethyl)amino)butanenitrile (9f): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (71%, 32.3 mg); R_f 0.15 (EtOAc/petroleum ether = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.04 (s, 1H), 4.41 (dd, *J* = 16.0, 10.2 Hz, 3H), 3.81 (q, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.19 – 2.02 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 136.4, 126.9, 122.3, 122.3, 119.6, 118.7, 118.4, 111.8, 111.3, 62.8, 45.1, 26.4, 24.7, 14.1 ppm. Spectral data match those previously reported.[17e]

4-(((Tetrahydrofuran-2-yl)methyl)amino)butanenitrile (9g): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (80%, 26.9 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 (s, 1H), 4.42 (t, *J* = 5.8 Hz, 2H), 4.09 – 4.05 (m, 1H), 3.91 – 3.86 (m, 1H), 3.84 – 3.75 (m, 1H), 3.73 – 3.63 (m, 1H), 3.47 – 3.29 (m, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.16 – 1.99 (m, 3H), 1.98 – 1.88 (m, 2H), 1.65 – 1.58 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 118.7, 77.6, 68.2, 62.8, 48.9, 28.6, 25.7, 24.8, 14.1 ppm; IR (neat): υ_{max} 3394, 2975, 2254, 1723, 1650, 1502,

1309, 1230, 1048, 880, 749 cm^{-1}; HRMS (ESI) calcd for $C_9H_{16}KN_2O$ $[M+K]^+$ 207.0894, found 207.0896.

4-(Cyclohexyleamino)butanenitrile (9h): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (78%, 25.9 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.42 (t, *J* = 5.8 Hz, 2H), 4.09 (d, *J* = 8.4 Hz, 1H), 3.80 – 3.59 (m, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.14 – 2.03 (m, 4H), 1.83 – 1.73 (m, 2H), 1.70 – 1.62 (m, 1H), 1.42 – 1.32 (m, 2H), 1.24 – 1.14 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 118.7, 62.8, 53.5, 34.5, 25.3, 24.8, 24.6, 14.1 ppm; IR (neat): υ_{max} 3436, 2962, 2249, 1723, 1649, 1501, 1260, 1076, 1025, 800 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{18}N_2Na$ $[M+Na]^+$ 189.1362, found 189.1358.

4-(Cyclopropylamino)butanenitrile (9i): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (77%, 19.1 mg); R_f 0.19 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.54 (s, 1H), 4.42 (t, *J* = 5.8 Hz, 2H), 2.94 (td, *J* = 6.6, 3.1 Hz, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.20 – 2.01 (m, 2H), 0.90 – 0.78 (m, 2H), 0.69 – 0.58 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 118.7, 62.9, 27.1, 24.8, 14.1, 8.7 ppm; IR (neat): υ_{max} 3365, 2962, 2251, 1723, 1652, 1500, 1313, 1247, 1026, 798 cm^{-1}; HRMS (ESI) calcd for $C_7H_{13}N_2$ $[M+H]^+$ 125.1073, found 125.1070.

Methyl 2-((3-cyanopropyl)amino)-2-(3a,7a-dihydro-1*H*-indol-3-yl)acetate (9j): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (34%, 18.5 mg); R_f 0.15 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 5.07 – 4.57 (m, 2H), 4.42 (t, *J* = 5.8 Hz,

2H), 3.72 (s, 3H), 3.40 (d, J = 5.3 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.16 – 2.06 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 172.3, 136.1, 127.2, 122.9, 122.5, 119.9, 118.7, 118.2, 111.3, 108.9, 63.0, 57.1, 52.6, 29.1, 24.7, 14.1 ppm; IR (neat): υ_{max} 3391, 2961, 2251, 1725, 1651, 1500, 1310, 1224, 1095, 1023, 799, 744 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}N_3O_2$ $[M+H]^+$ 286.1550, found 286.1544.

Methyl 3-((3-cyanopropyl)amino)propanoate (9k): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (65%, 22.1 mg); R_f 0.2 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.82 (s, 1H), 4.42 (t, J = 5.8 Hz, 2H), 3.76 (dd, J = 12.3, 6.4 Hz, 2H), 3.72 (s, 3H), 2.65 (t, J = 6.0 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 2.14 – 2.07 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 172.2, 118.7, 62.9, 51.9, 40.6, 34.6, 24.7, 14.1 ppm; IR (neat): υ_{max} 3368, 2959, 2250, 1723, 1647, 1500, 1306, 1226, 1028, 978, 799 cm^{-1}; HRMS (ESI) calcd for $C_8H_{14}KN_2O_2$ $[M+K]^+$ 209.0687, found 209.0684.

Methyl 4-((3-cyanopropyl)amino)butanoate (9l): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (68%, 25.0 mg); R_f 0.2 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.50 (s, 1H), 4.42 (t, J = 5.8 Hz, 2H), 3.69 (s, 3H), 3.61 – 3.50 (m, 2H), 2.54 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.18 – 2.06 (m, 2H), 2.00 – 1.93 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 173.5, 118.7, 62.9, 51.8, 44.7, 31.1, 25.6, 24.8, 14.1 ppm; IR (neat): υ_{max} 3368, 2962, 2250, 1721, 1648, 1500, 1306, 1260, 1094， 980， 799 cm^{-1}; HRMS (ESI) calcd for $C_9H_{20}N_3O_2$ $[M+NH_4]^+$ 202.1550, found 202.1545.

4-(Butyl(ethyl)amino)butanenitrile (9m): Following the Method D with the corresponding

cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (65%, 21.8 mg); R_f 0.35 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (t, *J* = 5.8 Hz, 2H), 3.43 – 3.19 (m, 4H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.21 – 2.00 (m, 2H), 1.54 – 1.46 (m, 2H), 1.33 – 1.28 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 118.6, 63.1, 51.7, 47.3, 30.3, 24.7, 19.8, 14.0, 13.7, 13.4 ppm; IR (neat): υ_{max} 2962, 2250, 1731, 1639, 1483, 1306, 1221, 989, 800 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{20}KN_2$ $[M+K]^+$ 207.1258, found 207.1260.

1-(3-Cyanopropyl)piperidine-4-carbonitrile (9n): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (64%, 22.6 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (t, *J* = 5.9 Hz, 2H), 3.61 – 3.47 (m, 2H), 3.30 (dd, *J* = 10.6, 6.6 Hz, 2H), 2.94 – 2.82 (m, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.21 – 1.93 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 120.8, 118.5, 63.4, 48.9, 29.0, 25.8, 24.7, 14.1 ppm; IR (neat): υ_{max} 2963, 2242, 1727, 1642, 1483, 1209, 1029, 798 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{19}N_4$ $[M+NH_4]^+$ 195.1604, found 195.1608.

4-Morpholinobutanenitrile (9o): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (66%, 20.3 mg); R_f 0.13 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (t, *J* = 5.9 Hz, 2H), 3.85 – 3.78 (m, 4H), 3.37 (dd, *J* = 6.1, 3.1 Hz, 4H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.16 – 2.09 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 118.6, 67.1, 63.3, 50.9, 24.7, 14.1 ppm; IR (neat): υ_{max} 2962, 2856, 2250, 1730, 1643, 1484, 1211, 1116, 990, 800 cm^{-1}; HRMS (ESI) calcd for $C_8H_{18}N_3O$ $[M+NH_4]^+$ 172.1444, found 172.1443.

4-(Pyrrolidin-1-yl)butanenitrile (9p): Following the Method D with the corresponding

cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (90%, 24.8 mg); R_f 0.2 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (t, *J* = 5.8 Hz, 2H), 3.73 – 3.68 (m, 4H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.18 – 2.06 (m, 2H), 2.00 – 1.87 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 118.8, 62.7, 51.5, 25.6, 24.8, 14.1 ppm; IR (neat): υ_{max} 2962, 2248, 1719, 1630, 1524, 1483, 1259, 1027, 799 cm^{-1}; HRMS (ESI) calcd for $C_8H_{15}N_2$ $[M+H]^+$ 139.1230, found 139.1228.

4-((((1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)amino)butanenitrile (9q): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (76%, 53.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.91 (s, 1H), 4.43 (t, *J* = 5.8 Hz, 2H), 4.23 (s, 1H), 3.48 (dd, *J* = 13.3, 7.3 Hz, 1H), 3.34 (dd, *J* = 13.3, 5.9 Hz, 1H), 2.98 – 2.92 (m, 1H), 2.88 – 2.76 (m, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.33 (d, *J* = 12.8 Hz, 1H), 2.15 – 2.03 (m, 2 H), 1.84 – 1.67 (m, 4H), 1.53 (dd, *J* = 14.8, 7.9 Hz, 2H), 1.47 – 1.31 (m, 2H), 1.25 (d, *J* = 2.2 Hz, 6H), 1.23 (s, 3H), 1.01 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.8, 145.7, 134.3, 126.8, 124.1, 124.0, 118.7, 62.8, 55.7, 45.7, 38.2, 38.0, 37.5, 35.7, 33.3, 30.0, 25.2, 24.8, 23.9, 18.9, 18.4, 18.2, 14.1 ppm; IR (neat): υ_{max} 3380, 2960, 2251, 1726, 1649, 1501, 1307, 1226, 1031, 803, 734 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{37}N_2$ $[M+H]^+$ 353.2951, found 353.2951.

4-(((3R,5S,7r)-3,5-dimethyladamantan-1-yl)amino)butanenitrile (9r): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (40%, 19.7 mg); R_f 0.3 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (t, *J* = 5.9 Hz, 2H), 3.94 (s, 1H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.22– 2.19 (m, 1H),

2.17 – 2.07 (m, 2H), 1.73 (s, 2H), 1.51 (dd, *J* = 27.8, 11.9 Hz, 4H), 1.34 (q, *J* = 12.3 Hz, 4H), 1.16 (s, 2H), 0.88 (s, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 118.6, 63.0, 56.1, 50.2, 49.5, 49.5, 49.4, 42.2, 41.8, 32.9, 30.4, 30.0, 24.8, 14.1 ppm; IR (neat): υ_{max} 2903, 2251, 1729, 1649, 1502, 1311, 1224, 1029, 798 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}N_2Na$ $[M+Na]^+$ 269.1988, found 269.1991.

4-(4-(9-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)butanenitrile (9s): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (74%, 55.8 mg); R_f 0.15 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.20 – 7.13 (m, 3H), 7.11 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.44 (t, *J* = 5.8 Hz, 2H), 3.60 – 3.32 (m, 4H), 3.22 (t, *J* = 9.8 Hz, 2H), 2.94 – 2.75 (m, 2H), 2.69 – 2.62 (m, 1H), 2.58 – 2.53 (m, 3H), 2.50 – 2.42 (m, 2H), 2.17 – 2.05 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 156.9, 146.7, 139.5, 137.5, 136.7, 134.4, 133.3, 132.9, 131.5, 130.5, 129.0, 126.1, 122.2, 118.6, 118.0, 114.2, 63.2, 52.0, 31.6, 31.6, 31.4, 31.4, 24.7, 14.1 ppm; IR (neat): υ_{max} 2924, 2854, 2252, 1729, 1640, 1482, 1300, 1210, 995, 733 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{24}ClN_3Na$ $[M+Na]^+$ 400.1551, found 400.1532.

4-(4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl)butanenitrile (9t): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (45%, 34.2 mg); R_f 0.13 (EtOAc/petroleum ether = 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.30 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.98 (td, *J* = 7.6, 1.7 Hz, 1H), 3.53 (s, 4H), 2.53 (t, *J* = 6.7 Hz, 6H), 2.46 (t, *J* = 7.1 Hz, 2H), 1.89 – 1.83 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101

MHz, $CDCl_3$): δ = 159.2, 158.8, 151.7, 140.1, 132.4, 130.2, 129.0, 127.0, 125.7, 124.9, 124.5, 122.6, 120.0, 119.6, 56.21, 52.85, 47.30, 22.65, 14.89. ppm; IR (neat): υ_{max} 2940, 2246, 1587, 1556, 1469, 1259, 1100, 1016, 774, 677 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}ClN_4O$ $[M+H]^+$ 381.1477, found 381.1471.

Characterization of Products 11

5-(Benzylamino)-5-phenylpentanenitrile (11a): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (45%, 23.8 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.26 (m, 10H), 6.11 – 5.88 (m, 1H), 4.65 (d, *J* = 5.4 Hz, 2H), 4.53 (s, 1H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.21 – 1.96 (m, 2H), 1.78 – 1.69 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 139.1, 138.0, 128.9, 128.6, 128.3, 128.0, 127.4, 126.3, 119.1, 99.9, 49.3, 35.3, 21.4, 16.9 ppm; IR (neat): υ_{max} 3369, 2961, 2247, 1720, 1649, 1499, 1360, 1229, 1048, 799, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}N_2Na$ $[M+Na]^+$ 287.1519, found 287.1532.

5-(benzylamino)-5-(o-tolyl)pentanenitrile (11b): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (68%, 37.8 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.31 (m, 6H), 7.24 – 7.15 (m, 3H), 6.22 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.65 (d, *J* = 6.1 Hz, 2H), 4.58 (s, 1H), 2.45 (s, 3H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.15 – 1.95 (m, 2H), 1.89 – 1.73 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.0, 137.7, 134.6, 130.5, 128.9, 127.9, 127.9, 127.4, 126.3, 125.7, 119.1, 73.0, 49.2, 34.6, 21.4, 19.1, 16.9 ppm; IR (neat): υ_{max} 3062, 2967, 2668, 2255, 1722, 1655, 1553, 1315, 1230, 989, 808, 734 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}N_2K$ $[M+K]^+$ 317.1415, found 317.1406.

5-(benzylamino)-5-(4-fluorophenyl)pentanenitrile (11c): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (40%, 22.5 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.28 (m, 7H), 7.10 – 7.01 (m, 2H), 5.97 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 2H), 4.56 (s, 1H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.21 – 2.08 (m, 1H), 2.07 – 1.95 (m, 1H), 1.87 – 1.65 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 138.0, 135.0 (d, *J* = 3.19), 128.9, 128.2, 128.1, 128.0, 127.4, 119.0, 115.7, 115.5, 75.6, 49.2, 35.3, 21.4, 16.9 ppm; IR (neat): υ_{max} 3569, 2969, 2255, 1732, 1653, 1510, 1326, 1232, 1001, 843, 645 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}FN_2K$ [M+K]$^+$ 321.1164, found 321.1178.

5-(benzylamino)-5-(naphthalen-2-yl)pentanenitrile (11d): Following the Method D with the corresponding cyclobutanone oxime ester (0.4 mmol) and aliphatic amine (0.2 mmol). Faint yellow liquid (52%, 32.6 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 13.7, 6.6 Hz, 4H), 7.54 – 7.47 (m, 3H), 7.41 – 7.35 (m, 2H), 7.35 – 7.29 (m, 3H), 6.17 (dd, *J* = 7.4, 5.7 Hz, 1H), 4.65 (d, *J* = 6.1 Hz, 2H), 4.54 (s, 1H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.30 – 2.20 (m, 1H), 2.18 – 2.08 (m, 1H), 1.88 – 1.69 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 138.0, 136.4, 133.1, 133.0, 128.9, 128.6, 128.0, 128.0, 127.6, 127.4, 126.4, 126.3, 125.7, 123.8, 119.1, 76.4, 49.3, 35.2, 21.4, 16.9 ppm; IR (neat): υ_{max} 3268, 2935, 2667, 2254, 1715, 1653, 1085, 990, 850, 759, 671 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}N_3$ [M+NH_4]$^+$ 332.2121, found 332.2100.

(E)-1-benzyl-2-(2-phenylcyclohexylidene)hydrazine (11e'): Faint yellow liquid (80%, 69.5 mg); R_f 0.16 (EtOAc/petroleum ether = 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.29 (m, 9H), 7.25 (dd, *J* = 9.1, 3.7 Hz, 1H), 4.65 (s, 3H), 3.96 (t, *J* = 4.9 Hz, 1H), 3.00 – 2.79 (m, 1H), 2.49 (dd,

J = 9.8, 4.2 Hz, 1H), 2.39 – 2.20 (m, 1H), 2.06 (td, *J* = 9.9, 5.0 Hz, 1H), 1.86 – 1.59 (m, 4H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 171.5, 138.7, 138.1, 128.8, 128.4, 127.8, 127.5, 127.3, 126.5, 49.1, 45.3, 31.0, 26.2, 25.5, 22.1 ppm; IR (neat): υ_{max} 3378, 2957, 2259, 1750, 1654, 1549, 1507, 1314, 1213, 975, 866, 735 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_2$ $[M+H]^+$ 279.1856, found 279.1853.

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10b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.19 (m, 4H), 4.28 (t, *J* = 8.1 Hz, 1H), 3.12 – 2.80 (m, 2H), 2.50 (s, 3H), 2.48 – 2.36 (m, 1H), 2.19 – 2.08 (m, 1H), 2.08 – 1.90 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 179.1, 156.3, 146.2 (m), 144.2 (m), 143.7 (m), 141.7 (m), 138.5, 136.1(m), 135.6, 130.1, 126.7, 126.4, 125.8, 107.0 (m), 46.3, 33.6, 30.4, 22.2, 19.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.2 (m, 2F), -148.1 (m, 1F), -160.0 (m, 2F) ppm; IR (neat): υ_{max} 3278, 2985, 2256, 1766, 1659, 1455, 1340, 1095, 1054, 885, 639 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}F_5NO_2$ $[M+H]^+$ 384.1017, found 384.1011.

10c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 0.6H), 7.26 – 7.22 (m, 1.4H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.97 (t, *J* = 7.6 Hz, 1H), 2.93 – 2.81 (m, 1H), 2.75 – 2.65 (m, 1H), 2.40 – 2.27 (m, 1H), 2.09 – 1.91 (m, 2H), 1.91 – 1.76 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 178.7, 161.7 (d, *J* = 243.9), 156.5, 146.9 (m), 143.9 (m), 138.9 (m), 136.3 (m), 135.2 (d, *J* = 3.26), 133.1 (m), 129.4 (d, *J* = 7.9), 115.4 (d, *J* = 23.2), 107.0 (m), 48.8, 34.8, 30.3, 22.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.8 (m, 1F), -137.1 (m, 2F), -147.9 (m, 1F), -159.9 (m, 2F) ppm; IR (neat): υ_{max} 3282, 2976, 2359, 1757, 1654, 1504, 1325, 1218, 858, 781 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{12}F_6NO_2$ $[M+H]^+$ 388.0767, found 388.0766.

10d: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 – 7.77 (m, 3H), 7.72 (s, 1H), 7.51 – 7.39 (m, 3H), 4.18

(t, J = 8.1 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.85 – 2.71 (m, 1H), 2.43 – 2.36 (m, 1H), 2.24 – 2.00 (m, 2H), 1.96 – 1.80 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 178.9, 156.6, 146.4 (m), 144.0 (m), 141.9 (m), 138.8 (m), 136.9, 136.3 (m), 133.2, 132.4, 128.3, 127.6, 127.5, 126.4, 126.1, 125.9, 125.7, 107.1 (m), 49.5, 34.5, 30.4, 22.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.2 (m, 2F), -147.9 (m, 1F), -160.0 (m, 2F) ppm; IR (neat): υ_{max} 3067, 2969, 1766, 1661, 1506, 1332, 1220, 1003, 859, 745 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{15}F_5NO_2$ $[M+H]^+$ 420.1017, found 420.1014.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc. XXXXX

^{1}H and ^{13}C spectra of all new compounds; the primary mechanistic studies of the reactions.

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REFERENCE

(1) For selected reviews, see: (a) *Amines: Synthesis Properties and Applications*; Lawrence, S. A., Ed.; Cambridge Univ. Press: Cambridge, U.K., 2004. (b) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (c) *Alkaloids: A Treasury of Poisons and Medicines*; Funayama, S., Cordell, G. A., Eds.; Academic Press: Waltham, MA, 2014. (d) Froidevaux, V.; Negrell, C.; Caillol, S.; Pascault, J.-P.; Boutevin, B. Biobased amines: from synthesis to polymers; present and future. *Chem. Rev.* **2016**, *116*, 14181.

(2) For selected reviews, see: (a) Hartwig, J. F. Evolution of a fourth generation catalyst for the amination and thioetherification of aryl halides. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Bariwal, J.; Van der Eycken, E. C-N bond forming cross-coupling reactions:an overview. *Chem. Soc. Rev.* **2013**, *42*, 9283. (c) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. *Chem. Soc. Rev.* **2014**, *43*, 3525. (d) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C-N cross-coupling reactions. *Chem. Rev.* **2016**, *116*, 12564. (e) Qiao, J. X.; Lam, P. Y. S. Copper-promoted carbon-heteroatom bond cross-coupling with boronic acids and derivatives. *Synthesis* **2011**, 829. and references cited therein.

(3) (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. Synthesis of secondary amines. *Tetrahedron* **2001**, *57*, 7785. (b) Abdel-Magid, A. F.; Mehrman, S. J. A review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes. *Org. Process Res. Dev.* **2006**, *10*, 971. (c) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. Mitsunobu and related reactions: advances and applications. *Chem. Rev*. **2009**, *109*, 2551. (d) Sorribes, I.; Junge, K., Beller, M. Direct catalytic *N*-alkylation of amines with carboxylic acids. *J. Am. Chem. Soc.* **2014**, *136*, 14314. (e) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J.

Late transition metal-catalyzed hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596. (f) Cheung, C. W.; Hu, X. Amine synthesis via iron-catalysed reductive coupling of nitroarenes with alkyl halides. *Nat. Commun*. **2016**, *7*, 12494. (g) Jagadeesh, R. V.; Murugesan, K.; Alshammari, A. S.; Neumann, H.; Pohl, M. M.; Radnik, J.; Beller, M. MOF-derived cobalt nanoparticles catalyze a general synthesis of amines. *Science* **2017**, *358*, 326. (h) Guo, X.; Wenger, O. S. Reductive amination by photoredox catalysis by polarity-matched hydrogen atom transfer. *Angew. Chem.*, *Int. Ed.* **2018**, *57*, 2469.

(4) For recent reviews and examples, see: (a) Kaga, A.; Chiba, S. Engaging radicals in transition metal-catalyzed cross-coupling with alkyl electrophiles: recent advances. *ACS Catal*. **2017**, *7*, 4697. (b) Fu, G. C. Transition-metal catalysis of nucleophilic substitution reactions: a radical alternative to S_n1 and S_n2 processes. *ACS Cent. Sci.* **2017**, *3*, 692. (c) Peacock, D. M.; Roos, C. B. and Hartwig, J. F. Palladium-catalyzed cross coupling of secondary and tertiary alkyl bromides with a nitrogen nucleophile. *ACS Cent. Sci.* **2016**, *2*, 647.

(5) (a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. Transition-metal-catalyzed alkylations of amines with alkyl halides: photoinduced, copper-catalyzed couplings of carbazole. *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 5129. (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. Photoinduced, copper-catalyzed alkylation of amides with unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **2014**, *136*, 2162. (c) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric copper-catalyzed C-N cross-couplings induced by visible light. *Science* **2016**, *351*, 681. (d) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-catalyzed alkylation of aliphatic amines induced by visible light. *J. Am. Chem. Soc.* **2017**, *139*, 17707. (e) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. Photoinduced, copper-catalyzed alkylation of amines: a mechanistic study of the cross-coupling of carbazole with alkyl bromides. *J. Am. Chem. Soc.* **2017**, *139*, 12716. (f) Ahn, J. M.; Peters, J. C.; Fu, G. C. Design of a photoredox catalyst that enables the direct synthesis of carbamate-protected primary amines via photoinduced, copper-catalyzed *N*-alkylation reactions of unactivated secondary halides. *J. Am. Chem. Soc.* **2017**, *139*, 18101.

(6) (a) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, copper-catalyzed decarboxylative C-N coupling to generate protected amines: an alternative to the curtius

rearrangement. *J. Am. Chem. Soc.* **2017**, *139*, 12153. (b) Liang, Y.; Zhang, X.; MacMillan, D. W. C. Decarboxylative sp^3 C-N coupling via dual copper and photoredox catalysis. *Nature* **2018**, *559*, 83. (c) Mao, R.; Frey, A.; Balon, J. and Hu, X. Decarboxylative C(sp^3)-N cross-coupling via synergetic photoredox and copper catalysis. *Nat. Catal.* **2018**, 1, 120. (d) Mao, R.; Balon, J.; Hu, X. Cross coupling of alkyl redox-active esters with benzophenone imines via tandem photoredox and copper catalysis. *Angew. Chem.*, *Int. Ed.* **2018**, *130*, 9501.

(7) For selected reviews, see: (a) Gansäuer, A.; Lauterbach, T.; Narayan, S. Strained heterocycles in radical chemistry. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 5556. (b) Kulinkovich, O. G. The chemistry of cyclopropanols. *Chem. Rev.* **2003**, *103*, 2597. (c) Rena, R.; Zhu, C. Radical-mediated ring-opening functionalization of cyclobutanols: a shortcut to γ-substituted ketones. *Synlett.* **2016**, *27*, 1139. (d) Wu, X.; Zhu, C. Recent advances in ring‐opening functionalization of cycloalkanols by C–C σ-bond cleavage. *Chem. Rec*. **2018**, *18*, 587. (e) Marek, I.; Masarwa, A.; Delaye, P. L.; Leibeling, M. Selective carbon-carbon bond cleavage for the stereoselective synthesis of acyclic systems. *Angew. Chem., Int. Ed*. **2015**, *54*, 414. (f) Shaw, M. H.; Bower, J. F. Synthesis and applications of rhodacyclopentanones derived from C–C bond activation. *Chem. Commun*. **2016**, *52*, 10817.

(8) (a) Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. New chemistry of iminyl radicals. *J. Chem. Soc. Chem. Commun*., **1975**, 291; (b). Forrester, A. R.; Gill, M.; Thomson, R. H. Synthetic reactions with iminyl radicals. *J. Chem. Soc. Chem. Commun*., **1976**, 677; (c) Forrester, A. R.; Gill, M.; Napier, R. J.; Thomson, R. H. Iminyls. Part 5. Intramolecular hydrogen abstraction by alkyl(ary1)-iminyls. A new tetralone synthesis. *J. Chem. Soc. Perkin Trans.,* **1979**, *1* 632; (d) Boivin, J.; Fouquet, E.; Zard, S. Z. Ring opening induced by iminyl radicals derived from cyclobutanones: new aspects of tin hydride cleavage of S-phenyl sulphenylimines. *J. Am. Chem. Soc.* **1991**, *113*, 1055. (e) Boivin, J.; Fouquet, E.; Zard, S. Z. Iminyl radicals: part II. ring opening of cyclobutyl- and cyclopentyliminyl radicals. *Tetrahedron* **1994**, *50*, 1757. (f) Boivin, J.; Fouquet, E.; Zard, S. Z. A new and synthetically useful source of iminyl radicals. *Tetrahedron Lett.* **1991**, *32*, 4299. (g) Nishimura, T.; Yoshinaka, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. Iridium-catalyzed ring cleavage reaction of cyclobutanone *O*-benzoyloximes providing nitriles. *Org. Lett.* **2005**, *7*, 2425. (h) Faulkner, A.; Race, Nicholas J.; Scottb, J. S.; Bower, J. F. Copper catalyzed Heck-like cyclizations of oxime esters. *Chem. Sci.* **2014**, *5*, 2416.

(9) For selected examples, see: (a) Yang, H.-B.; Selander, N. Divergent iron-catalyzed coupling of *O*-acyloximes with silyl enol ethers. *Chem. Eur. J.* **2017**, *23*, 1779. (b) Zhao, B.; Shi, Z. Copper-catalyzed intermolecular Heck-like coupling of cyclobutanone oximes initiated by selective C-C bond cleavage. *Angew. Chem.*, *Int. Ed.* **2017**, *56*, 12727. (c) Li, L.; Chen, H.; Mei, M.; Zhou, L. Visible-light promoted γ-cyanoalkyl radical generation: three-component cyanopropylation/ etherification of unactivated alkenes. *Chem. Commun.* **2017**, *53*, 11544. (d) Gu, Y.-R.; Duan, X.-H.; Yang, L.; Guo, L.-N. Direct C−H cyanoalkylation of heteroaromatic N−oxides and quinones via C-C bond cleavage of cyclobutanone oximes. *Org. Lett.* **2017**, *19*, 5908. (e) Yu, X.-Y.; Chen, J.-R.; Wang, P.-Z.; Yang, M.-N.; Liang, D.; Xiao, W.-J. Visible light-driven iminyl radical-mediated C-C single bond cleavage/radical addition cascade of oxime esters. *Angew. Chem.*, *Int. Ed.* **2018**, *57*, 738. (f) Yang, L.; Gao, P.; Duan, X.-H.; Gu, Y.-R.; Guo, L.-N. Direct C−H cyanoalkylation of quinoxalin-2(1*H*)-ones via radical C-C bond cleavage. *Org. Lett.* **2018**, *20*, 1034. (g) Zhang, J.-Y.; Duan, X.-H.; Yang, J.-C.; Guo, L.-N. Redox-neutral cyanoalkylation/cyclization of olefinic 1,3-dicarbonyls with cycloketone oxime esters: access to cyanoalkylated dihydrofurans. *J. Org. Chem.* **2018**, *83*, 4239. (h) Zhao, J.-F.; Duan, X.-H.; Gu, Y.-R.; Gao, P.; Guo, L.-N. Iron-catalyzed decarboxylative olefination of cycloketone oxime esters with *α,β*-unsaturated carboxylic acids via C−C bond cleavage. *Org. Lett.* **2018**, *20*, 4614. and references cited therein.

(10) For examples concerning C-X and C-Y bond formations: (a) Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Photoinduced remote functionalizations via iminyl radical promoted C-H and C-C bond cleavage cascades. *Angew. Chem.*, *Int. Ed.* **2018**, *57*, 744. (b) Ai, W.; Liu, Y.; Wang, Q.; Lu, Z.; Liu, Q. Cu-catalyzed redox-neutral ring cleavage of cycloketone *O*-acyl oximes: chemodivergent access to distal oxygenated nitriles. *Org. Lett.* **2018**, *20*, 409. (c) Zhao, B.; Chen, C.; Lv, J.; Li, Z.; Yuan, Y.; Shi, Z. Photoinduced fragmentation-rearrangement sequence of cycloketoxime esters. *Org. Chem. Front.* **2018**, *5*, 2719. (d) Jackman, M. M.; Im, S.; Bohman, S. R.; Lo, C. C. L.; Garrity, A. L.; Castle, S. L. Synthesis of functionalized nitriles by microwave-promoted fragmentations of cyclic iminyl radicals. *Chem. Eur. J.* **2018**, *24*, 594. (e) Yu, X.-Y.; Wang, P-Z.; Yan, D.-M.; Lu, B. Chen, J.-R.; Xiao, W.-J. Photocatalytic neophyl rearrangement and reduction of distal carbon radicals by iminyl radical-mediated C-C bond cleavage. *Adv. Synth. Catal*. **2018**, *360*, 3601. (f) Zhao, B.; Tan, H.;

Chen, C.; Jiao, N.; Shi, Z. Photoinduced C-C bond cleavage and oxidation of cycloketoxime esters. *Chin. J. Chem.* **2018**, *36*, 995. (g) Zhang, J.-J.; Duan, X.-H.; Wu, Y.; Yang, J.-C.; Guo, L.-N. Transition-metal free C-C bond cleavage/borylation of cycloketone oxime esters. *Chem. Sci.* **2018**, *10*, 161. (h) During the revision of this manuscript (first submitted date: 23-Oct-2018), a similar work reported, in their paper only anilines and few heteroaromatic amines have been investigated therein. In our reports, a variety of (hetero)aromatic amines, aromatic *N*-heterocycles, sulfonamides, aliphatic amines, especially natural products, amino acid esters and drugs are amenable. Furthermore, less strained 2-substituted cyclopentanone oxime esters were also suitable substrates in our reaction, for details, see: Min, Q-Q.; Li, N.; Chen, G-L.; Liu, F. Copper-catalysed C(sp3)–N coupling initiated by selective C–C bond cleavage of cyclobutanone oxime esters. *Org. Chem. Front.,* **2019**, *6*, 1200.

(11) For palladium-catalyzed ring-opening of cyclobutanone oxime esters, see: (a) Nishimura, T.; Uemura, S. Palladium(0)-catalyzed ring cleavage of cyclobutanone oximes leading to nitriles via *β*-carbon elimination. *J. Am. Chem. Soc.* **2000**, *122*, 12049. (b) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. Palladium-catalyzed transformation of cyclobutanone *O*-benzoyloximes to nitriles via C-C bond cleavage. *J. Org. Chem.* **2004**, *69*, 5342.

(12) For some examples on natural products or pharmaceuticals containing cyanoalkyl moieties, see: (a) *Chemistry of the Cyano Group* (Eds.: Z. Pappoport, S. Patai), Wiley: London, 1970. (b) Fleming, F. F. Nitrile-containing natural products. *Nat. Prod. Rep.* **1999**, *16*, 597. (c) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902.

(13) For selected examples using diketones as ligands in copper-catalyzed C-O or C − N formation reactions reactions, see: (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. Ullmann diaryl ether synthesis: rate acceleration by 2,2,6,6-tetramethylheptane-3,5-dione. *Org. Lett.* **2002**, *4*, 1623. (b) Shafir, A.; Buchwald, S. L. Highly selective room-temperature copper-catalyzed C-N coupling reactions. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (c) de Vries, J.; de Lange, B.; Lambers-Verstappen, M.; Schmieder-vande Vondervoort, L.; Sereinig, N.; de Rijk, R.; de Vries, A. Aromatic amination of aryl bromides catalysed by copper/*β*-diketone catalysts: the effect of concentration. *Synlett* **2006**, 3105. (d)

Shafir, A.; Lichtor, P. A.; Buchwald, S. L. N- versus O-arylation of aminoalcohols: orthogonal selectivity in copper-based catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 3490.

(14) For selected reviews concerning Pybox as ligands in transition-metal catalyzed reactions, see: (a) Desimoni, G.; Faita, G.; Quadrelli, P. Pyridine-2,6-bis(oxazolines), helpful ligands for asymmetric catalysts. *Chem. Rev.* **2003**, *103*, 3119. (b) Brittain, W. D. G.; Buckley, B. R.; Fossey, J. S. Asymmetric copper-catalyzed azide−alkyne cycloadditions. *ACS Catal*. **2016**, *6*, 3629. (c) Rohit, K. R.; Ujwaldev, S. M.; Saranya, S.; Anilkumar, G. Recent advances in the creation of asymmetric carbon centre(s) by generation of carbon-heteroatom bond(s) using metal-pybox complexes. *Asian J. Org. Chem.* **2018**, *7*, 2338. (d) Fernandez-Hernandez, J.; Ladouceur, S.; Shen, Y.; Iordache, A.； Wang, W.; Donato, L.; Gallagher-Duva, S.; De Anda Villa, M.; Slinker, J. D.; De Cola, L.; Zysman-Colman, E. Blue light emitting electrochemical cells incorporating triazole-based luminophores. *J. Mater. Chem. C,* **2013**, *1*, 7440; (e) Devery III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Flowers II, R. A.; Stephenson, C. R. J. Ligand functionalization as a deactivation pathway in a fac-Ir (ppy) 3-mediated radical addition. *Chem. Sci.,* **2015**, *6*, 537.

(15) (a) Armaroli, N.; Accorsi, G.; Cardinali, F.; Listorti, A. Photochemistry and photophysics of coordination compounds: copper. *Top. Curr. Chem.* **2007**, *280*, 69. (b) Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. Computational explorations of mechanisms and ligand-directed selectivities of copper-catalyzed Ullmann-type reactions. *J. Am. Chem. Soc.* **2010**, *132*, 6205. (c) Yu, H.-Z.; Jiang, Y.-Y.; Fu, Y.; Liu, L. Alternative mechanistic explanation for ligand-dependent selectivities in copper-catalyzed *N*- and *O*-arylation reactions. *J. Am. Chem. Soc.* **2010**, *132*, 18078. (d) Franc, G.; Cacciuttolo, Q.; Lefevre, G.; Adamo, C.; Ciofini, I.; Jutand, A. Mechanistic insights into C-N coupling catalyzed by 1,3-diketonate ligated copper: unprecedented activation of aryl iodide. *ChemCatChem* **2011**, *3*, 305. (e) Lefevre, G.; Franc, G.; Adamo, C.; Jutand, A.; Ciofini, I. Influence of the formation of the halogen bond ArX─N on the mechanism of diketonate ligated copper-catalyzed amination of aromatic halides. *Organometallics* **2012**, *31*, 914. (f) Paria, S.; Reiser, O. Copper in photocatalysis. *ChemCatChem* **2014**, *6*, 2477. (g) Giri, R.; Brusoe, A.; Troshin, K.; Wang, J. Y.; Font, M.; Hartwig, J. F. Mechanism of the Ullmann biaryl ether synthesis catalyzed by complexes of anionic ligands: evidence for the reaction of iodoarenes with ligated anionic Cu^{I} intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 793.

(16) A possible mechanism has been given in the Supporting Information (for details, see S39).

(17) (a) Xu, H.-J.; Zhu, F.-F.; Shen, Y.-Y.; Wan X.; Feng, Y.-S. Baeyer–villiger oxidation of cyclobutanones with 10-methylacridinium as an efficient organocatalyst. *Tetrahedron.,* **2012**, *68*, 4145. (b) Millet, A.; Lefebvre, Q.; Rueping, M. Visible-light photoredox-catalyzed giese reaction: decarboxylative addition of amino acid derived α-amino radicals to electron-deficient olefins. *Chem. Eur. J.,* **2016**, *22*, 13464. (c) Díaz, J. E.; Mollo, M.C.; Orelli, L. R. Microwave-assisted cyclizations promoted by polyphosphoric acid esters: a general method for 1-aryl-2-iminoazacycloalkanes. *Beilstein J. Org. Chem.,* **2016**, *12*, 2026. (d) Mangelinckx, S.; D'hooghe,M.; Peeters, S.; Kimpe, N. D. Synthesis of 2-[(arylmethylene) amino] cyclopropanecarbonitriles via a two-step ring transformation of 2-(cyanomethyl) aziridines. *Synthesis,* **2009**, *7*, 1105. (e) Pakhare, D. S.; Kusurkar, R. S. Synthesis of tetrahydro-β-carbolines, β-carbolines, and natural products, (±)-harmicine, eudistomin U and canthine by reductive Pictet Spengler cyclization. *Tetrahedron Lett.,* **2015**, *56*, 6012.